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Poster

648. Cell Cycle Mechanisms in Neurogenesis II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 648.01/DP01/A1 (Dynamic Poster)

Topic: A.01. Neurogenesis and Gliogenesis

Support: NINDS R01NS076640

Title: Dissecting cytokinesis defects in the Kif20b model of microcephaly

Authors: *K. C. MCNEELY[1], J. N. LITTLE[1], N. D. DWYER[2]
[1]Cell Biol., Univ. of Virginia, Charlottesville, VA; [2]Cell Biol., Univ. of Virginia, CHARLOTTESVILLE, VA

Abstract: Neural stem cells (NSCs) must undergo polarized cell division within the ventricular zone to produce enough neurons to build the cortex. This specialized cell division must be intricately controlled to form a normal sized and layered cortex. Cytokinesis, the last step of cell division, controls the segregation of cytoplasm, membrane, and organelles to the two daughter cells through cleavage furrowing and establishment of a dense microtubule structure, the midbody. The midbody must be severed on one or both sides to finally separate the two daughter cells. Recently, cytokinesis has been implicated in cell fate determination, but the specialized mechanisms of cytokinesis in the developing brain remain unclear. We hypothesize that temporal and structural changes in cytokinesis of embryonic NSC may lead to changes in cell fate.
We previously reported a novel mouse model of microcephaly resulting from mutation of the Kinesin-6 family member Kif20b. Kif20b is a plus-end microtubule motor that localizes to the central spindle and midbody during cytokinesis. The *Kif20b -/-* mutant embryos have smaller and thinner cortices, reduced neurogenesis, and increased apoptosis. Additionally, the mutant NSC midbodies, observed at the ventricular surface, are wider, longer, and misoriented, suggesting defects in late cytokinesis.
In this work, we used both a knockdown of Kif20b in a human cell line and mouse mutant NSC cultures to study the precise role of this motor protein in cytokinesis. This work will help to elucidate the etiologies of microcephaly. Using live cell imaging and Silicone-Rhodamine Tubulin (SiR-tubulin), we found that knocking down KIF20B in HeLa cells resulted in changes in the timing of cleavage furrowing and abscission. Additionally, the midbodies of KIF20B knockdown cells showed changes in microtubule structure, supporting a role for Kif20b in midbody organization prior to abscission. To further explore the role Kif20b plays in NSC cell division we used an *in vitro* cortical NSC culture. In the NSC cultures, we found midbody shape defects including longer midbodies. Similar to the wider, longer midbodies observed *in vivo*, this supports a role for Kif20b in establishing or maintaining midbody structure. The NSC culture system also models the increased apoptosis seen *in vivo*, and shows that the apoptotic cells are

NSCs. These findings validate the *in vitro* system for studying NSC cytokinesis, and confirm a cell-autonomous role for Kif20b in NSC divisions. Currently, we are using this *in vitro* system to study detailed cytoskeletal structure and temporal dynamics of normal and abnormal cytokinesis in cerebral cortex development.

Disclosures: K.C. McNeely: None. **J.N. Little:** None. **N.D. Dwyer:** None.

Poster

648. Cell Cycle Mechanisms in Neurogenesis II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 648.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R01 NS083897

Title: Mitotically delayed Radial Glial stem cells and altered fate decisions in the developing cortex

Authors: *A. M. MITCHELL-DICK, L.-J. PILAZ, D. L. SILVER
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Abstract: Cortical pyramidal neurons are generated in development by embryonic neural stem cells termed Radial Glial cells (RGCs). During embryonic mouse corticogenesis RGCs divide both symmetrically and asymmetrically to produce excitatory neurons, RGCs, and intermediate progenitors (IPs). Yet how individual RGCs make asymmetric and symmetric fate decisions to pattern the cortex is incompletely understood. Investigation of this process will yield insight into cognitive disorders, including microcephaly, as defects in RGC divisions can lead to microcephaly. We have recently discovered using both genetic and pharmacological models that prolonged RGC mitosis results in increased asymmetric neurogenic divisions at the expense of proliferative divisions. These models recapitulate phenotypes observed in microcephaly, namely precocious neuron generation, loss of progenitors, and apoptosis. However, despite these advances the timing and degree to which prolonged mitosis impacts embryonic neurogenesis and imparts microcephaly phenotypes *in vivo* is unknown. Therefore, we sought to develop a model of inducible pharmacological delay *in vivo* to study the effects of directly prolonging mitosis. Here, using a recently developed method to lineage trace cells in the developing cortex, we establish an *in vivo* assay for investigating pharmacological RGC mitosis delay directly impacts cell fate. We first define the kinetics by which pharmacological delay impairs progenitor mitosis. We demonstrate that delayed RGCs *in vivo* generate an increased number of immature neurons, and more apoptosis in a subset of delayed progeny. These outcomes are at the expense of Pax6+ RGCs, as we observe less newborn progenitors following delay. Our ongoing work takes an unbiased approach to examine delayed cells and their progeny in order to elucidate mechanisms

of altered fate decisions and cellular response to prolonged mitosis. This model will provide a basis for understanding the pathways and cellular behaviors that underlie cognitive developmental disorders including microcephaly.

Disclosures: **A.M. Mitchell-Dick:** None. **L. Pilaz:** None. **D.L. Silver:** None.

Poster

648. Cell Cycle Mechanisms in Neurogenesis II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 648.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: NINDS R01NS076640

NIH 2T32GM008136-31A1

Title: p53 deletion rescues cerebral cortex growth in a genetic model of microcephaly

Authors: J. N. LITTLE[1], *N. DWYER[2]
[1]Cell Biol., [2]Cell Biol, Univ. of Virginia Sch. of Med., Charlottesville, VA

Abstract: Growth of the cerebral cortex requires precise divisions of neuroepithelial stem cells (NSCs) that undergo both symmetric and asymmetric divisions to first expand the progenitor pool and then produce post-mitotic neurons. How this is mediated is poorly understood. One consequence of impaired NSC proliferation is microcephaly, or a small brain. In a novel mouse model for microcephaly discovered by our lab, the mutation of the kinesin Kif20b results in reduced brain size at birth. Interestingly, we found abnormalities in cytokinesis of NSCs and increased apoptosis in *Kif20b-/-* cortex. Additionally, cortical pyramidal neurons are reduced in number and show defects in polarization and morphology. During cytokinesis, daughter cells separate their cytoplasm and cleave apart. This process requires formation of a cleavage furrow that ingresses to form the midbody, the last connection between two cells before the final separation event, called abscission. NSCs undergo a polarized form of cytokinesis within the neuroepithelium that is poorly understood. In the *Kif20b-/-* cortex, NSC midbodies at the apical membrane were misshapen and misaligned. These novel phenotypes suggest delays or failures in abscission. Our hypothesis is that the loss of Kif20b causes impaired cytokinesis that results in apoptosis in a subset of NSCs, depleting the progenitor pool and impairing neurogenesis.
To test our model for the etiology of *Kif20b-/-* microcephaly, we set out to prevent apoptosis of NSCs and observe whether microcephaly could be rescued. We crossed the *Kif20b* mutant mouse line to knockouts for the pro-apoptotic *Trp53* (gene encoding the tumor suppressor p53) and *Bax*. We found that p53 deletion rescues microcephaly in *Kif20b-/-* mice, but Bax deletion does not. p53 but not Bax deletion rescued the elevated apoptosis seen in *Kif20b-/-* brains, providing

further evidence for the central role of apoptosis in *Kif20b-/-* microcephaly. In addition to rescuing brain size, deletion of p53 rescued neonatal lethality in *Kif20b-/-* mice. However, *Kif20b-/- p53-/-* mice have reduced survival after birth, with some mice dying from hydrocephalus, suggesting that brain abnormalities still remain. Current work is focused on determining 1) if the final brain structure and lamination of double mutant mice are normal, 2) the relationship between cytokinesis defects and p53 activation in *Kif20b-/-* mice and 3) the consequence of cytokinesis failure for undead NSCs and neuron daughters when apoptosis is inhibited.

Disclosures: J.N. Little: None. **N. Dwyer:** None.

Poster

648. Cell Cycle Mechanisms in Neurogenesis II

Location: Halls A-C

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH grant NS028478

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Title: Symmetric cell divisions drive adult V-SVZ neurogenesis and stem cell maintenance

Authors: *K. OBERNIER[1], A. CEBRIAN-SILLA[3], M. THOMSON[2], J. PARRAGUEZ[1], J. M. GARCIA-VERDUGO[3], A. ALVAREZ-BUYLLA[4]
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Abstract: Neural stem cells (NSCs; B1 cells) persist in the ventricular-subventricular zone (V-SVZ) of the adult mammalian brain. B1 cells contact the lateral ventricle via a small apical ending, and blood vessels with a long basal process. B1 cells generate transient amplifying C cells that in turn give rise to young neurons that migrate to the olfactory bulb where they differentiate into interneurons. In contrast to classical views suggesting that neurogenesis and NSC maintenance are achieved by asymmetric self-renewal, we show here that B1 cells only

undergo symmetrical divisions in the adult mouse V-SVZ in vivo. The majority of B1 cells undergo symmetric consuming divisions producing C cells, which leads to a drastic decline in the number of B1 cells with increasing age. However, a subpopulation (~20-25%) of B1 cells self-renew, giving rise to two secondary B1 cells, which maintain the potential to self-renew again. Ex vivo live imaging of V-SVZ whole-mount preparations shows that during self-renewing cell divisions B1 cells maintain their basal process. Interestingly, in vivo, B1 cells also give rise to B2 cells. Similar to B1 cells, B2 cells are astrocytic and contact the vasculature, but lack the contact with the lateral ventricle. While the number of apical B1 cells is drastically reduced as mice age, B2 cells become the preponderant label-retaining cells over time. Although it is unknown whether B2 cells are neurogenic, we show that the population of secondary B (B1/B2) cells contains bona fide
stem cells as they stochastically contribute interneurons to the olfactory bulb later in life via consuming divisions. Importantly, the reactivation of secondary B cells can occur after several months, indicating that a subpopulation of self-renewing B cells is long-lived and contributes neurons to the olfactory bulb after extended periods of time.
This study identifies the cellular mechanism sustaining V-SVZ/OB neurogenesis throughout life.

Disclosures: **K. Obernier:** None. **A. Cebrian-Silla:** None. **M. Thomson:** None. **J. Parraguez:** None. **J.M. Garcia-Verdugo:** None. **A. Alvarez-Buylla:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics.

Poster

648. Cell Cycle Mechanisms in Neurogenesis II

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Program#/Poster#: 648.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSFC Grant 31571043

NSFC Grant 81571212

MOST Grant 2016YFA0101402

Title: Mir-203 interplays with polycomb repressive complexes to regulate the proliferation of neural stem/progenitor cells

Authors: ***Z. TENG**[1], P.-P. LIU[1], G.-B. TANG[2], Y.-J. XU[3], S.-F. ZHANG[3], Y.-Q. ZENG[1], H.-Z. DU[1], C.-M. LIU[1]
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Abstract: The polycomb repressive complex 1 (PRC1) and 2 (PRC2) are two distinct polycomb group (PcG) proteins that maintaining the stable silencing of specific sets of genes through chromatin modifications. Although the PRC2 component EZH2 has been known as an epigenetic regulator in promoting the proliferation of neural stem/progenitor cells (NSPCs), its regulatory network that control this process remains largely unknown. Here we show that miR-203 is repressed by EZH2 in both embryonic and adult NSPCs. MiR-203 negatively regulates the proliferation of NSPCs. One of PRC1 components, *Bmi1*, is a downstream target of miR-203 in NSPCs. Conditional knockout of *Ezh2* results in decreased proliferation ability of both embryonic and adult NSPCs. Meanwhile ectopic overexpression of BMI1 rescues the proliferation defects exhibited by miR-203 overexpression or EZH2 deficiency in NSPCs. Therefore, this study provides the evidence for coordinated function of the EZH2-miR-203-BMI1 regulatory axis that regulating the proliferation of NSPCs.

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Poster

648. Cell Cycle Mechanisms in Neurogenesis II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 648.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: BFU2015-66041-P

Title: Pallial neurogenesis in Xenopus laevis

Authors: N. MORENO[1], S. JIMENEZ[2], N. VIDAL[2], D. LOZANO[2], R. MORONA[2], J. M. LOPEZ[2], *A. GONZALEZ[3]
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Abstract: The complexity of the pallium during evolution has increased dramatically in many different respects. The highest level of complexity is found in mammals, where most of the pallium (cortex) shows a layered organization and neurons are generated during development following an inside-out order, a sequence not observed in other amniotes (birds and reptiles). Species-differences may be related to major neurogenetic events, from the neural progenitors that divide and produce all pallial cells. In mammals, two main types of precursors have been described, primary precursor cells in the ventricular zone (also called radial glial cells or apical

progenitors) and secondary precursor cells (called basal or intermediate progenitors) separated from the ventricle surface. Previous studies suggested that pallial neurogenetic cells, and especially the intermediate progenitors, evolved independently in mammalian and sauropsid lineages. In the present study, we examined pallial neurogenesis in the amphibian *Xenopus laevis*, a representative species of the only group of tetrapods that are anamniotes. The pattern of pallial proliferation during embryonic and larval development was studied, together with a multiple immunohistochemical analysis of putative progenitor cells. We found that there are two phases of progenitor divisions in the developing pallium that, following the radial unit concept from the ventricle to the mantle, finally result in an outside-in order of mature neurons, what seems to be the primitive condition of vertebrates. Gene expressions of key transcription factors that characterize radial glial cells in the ventricular zone were demonstrated in *Xenopus*. In addition, although mitotic cells were corroborated outside the ventricular zone, the expression pattern of markers for intermediate progenitors differed from mammals.

Disclosures: N. Moreno: None. **S. Jimenez:** None. **N. Vidal:** None. **D. Lozano:** None. **R. Morona:** None. **J.M. Lopez:** None. **A. Gonzalez:** None.

Poster

648. Cell Cycle Mechanisms in Neurogenesis II

Location: Halls A-C

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Program#/Poster#: 648.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Title: Nox4 participates in damage-induced proliferation of neural stem cells and subsequent restoration of recognition memory in the hippocampus

Authors: *Y. YOSHIKAWA[1], T. AGO[1], J. KURODA[1], Y. WAKISAKA[1], H. NAKASHIMA[2], K. NAKASHIMA[2], T. KITAZONO[1]
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Abstract: Purpose: It is known that reactive oxygen species (ROS) participate in growth regulation of neural stem cells (NSCs) and in hippocampus-associated learning and memory. However, the origin of ROS linking to these functions remains unknown. We found that Nox4, a ROS-producing NADPH oxidase family protein, is expressed in primary cultured NSCs and in Sox2-positive NSCs in the subventricular zone and in the subgranular zone (SGZ) of the hippocampus *in vivo*. In the present study, we investigated the roles of Nox4 in NSCs *in vitro* and *in vivo*.
Method: NSCs were prepared from telencephalons of pregnant ICR mouse embryos at E14.5. We overexpressed Nox4 in cultured NSCs by using lentivirus. We assessed proliferation of NSCs by MTT assay *in vitro* and by incorporation of 5-ethynyl-2’-deoxyuridine (EdU) *in vivo*.

Hippocampal neuronal damages were induced by intraperitoneal administration of trimethyltin (TMT) (2.1 mg/kg). Recognition memory was assessed by a novel object recognition (NOR) test. **Results:** Basic fibroblast growth factor (bFGF) significantly induced the phosphorylation of Akt and increased the proliferation of the cultured NSCs. Nox4 inhibitors, VAS2870 or GKT137831, as well as LY294002, an inhibitor of PI3K upstream of Akt, attenuated the bFGF-induced proliferation of the NSCs in a dose-dependent manner. Lentivirus-mediated Nox4 overexpression increased the production of H_2O_2, the phosphorylation of Akt, and the proliferation of the NSCs, while the enhanced proliferation was canceled by the presence of the Nox4 inhibitors. The differentiation into neurons or astrocytes was not different between cultured NSCs prepared from Nox4-deficient mice and those from wild-type littermates. Although the hippocampal development was apparently normal, the proliferation of NSCs in the SGZ in response to TMT-induced hippocampal neuronal damages was significantly attenuated in Nox4-deficient mice. A NOR test demonstrated that functional restoration of recognition memory after TMT-induced hippocampal neuronal damages was significantly attenuated in Nox4-deficient mice, compared with wild-type littermates.
Conclusion: Nox4 participates in the proliferation of NSCs both *in vitro* and *in vivo*. Nox4-mediated proliferation of NSCs in the SVZ of the hippocampus may be involved in post-damage functional restoration of recognition memory.

Disclosures: Y. Yoshikawa: None. **T. Ago:** None. **J. Kuroda:** None. **Y. Wakisaka:** None. **H. Nakashima:** None. **K. Nakashima:** None. **T. Kitazono:** None.

Poster

648. Cell Cycle Mechanisms in Neurogenesis II

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5T32MH079785-08

NIH Grant 5P30MH092177-07

Title: HIV-1 Tg26 transgenic mice exhibit early and late neurogenic deficits, which correlate with neurocognitive dysfunction

Authors: *R. PUTATUNDA, M. CURTIS, Y. ZHANG, T. ZHANG, X. XIAO, M. XIN, F. LI, D. PRATICO, M. F. BARBE, W. HU
Pathology and Lab. Med., Lewis Katz Sch. of Med. At Temple Univ., Philadelphia, PA

Abstract: Mild to moderate forms of HIV-1 associated neurocognitive disorders (HAND) continue to afflict HIV-1 infected patients even in the era of the combined antiretroviral therapy.

Recently, compromised adult neurogenesis has been shown to be an underlying substrate for HAND. Not only is HIV-1 capable of infecting neural stem cells (NSCs) *in vitro* and *in vivo*, the viral proteins Tat or gp120 have been shown to individually inhibit NSC proliferation and neuronal differentiation. However, no studies have characterized whether and how the combined viral proteins from latent HIV-1 reservoirs affect the early and late stages of neurogenesis, and correlated these changes with neurocognitive function. To this end, we performed *in vitro* and *in vivo* studies using HIV Tg26 transgenic mice expressing 7 of the 9 HIV-1 viral proteins. RT-qPCR analysis validated the presence of the Gag, Env, and Tat transcripts in the neurogenic zones. *In vitro* stemness assays revealed that Tg26 mouse NSCs were unable to form as many primary and secondary neurospheres as wild-type (WT) mouse NSCs. Additionally, i*n vitro* differentiation assays revealed that Tg26 mouse NSCs were not only unable to differentiate as efficiently into neurons as WT mouse NSCs, but they generated more astrocytes. These proliferative and differentiative effects were confirmed by immunohistochemistry in the dentate gyri of WT and Tg26 mice. Retroviral-eGFP labeling demonstrated that the newborn neurons in the dentate gyri of adult Tg26 mice had initial dendritic arborization deficits, as well as a slightly shorter dendritic length. Finally, Barnes Maze analysis revealed spatial memory acquisition and long term memory retention deficits in Tg26 mice. In conclusion, Tg26 mice exhibit early and late neurogenic deficits, which correlate with neurocognitive dysfunction. (This work was partially supported by a Ruth L. Kirchstein National Research Service Award NIH T32MH079785 (RP) and 5P30MH092177-07 (MFB))

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Poster

648. Cell Cycle Mechanisms in Neurogenesis II

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Program#/Poster#: 648.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: 2P01 CA085878-10A1

1R01 NS053900

Title: Clonal evolution from neural stem cells to glioblastoma in murine models

Authors: ***Y. ZHU**[1], Y. LI[2], B. LI[3], Y. WANG[2], S. AKGUL[2], B. ROSS[4], J. LI[4]
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Abstract: Over 90% of glioblastoma (GBM), the most common and lethal brain cancer in adults, develop rapidly with clinical evidence of lower-grade gliomas, thus also known as primary/de novo GBM. Due to rapid clinical course, little or no evidence is available on the existence of less aggressive or proliferative glioma precursor cells during early stages of primary GBM pathogenesis. Whether a therapeutic strategy can be developed to treat highly aggressive primary GBM at early stages remains unknown. Recent characterization of spatiotemporal genomic architecture of primary GBM suggests a clinically unobserved common ancestor (CA) with a less aggressive phenotype that could remain latent for decades. This CA generates genetically highly divergent subclones, seeding pre-therapy multifocal and/or post-therapy distally recurred GBMs. Here we developed mouse models of malignant gliomas/GBMs driven by single *p53* mutations, recapitulating this unique branched evolutionary pattern. We show a CA-derived malignant gliomas/GBMs, seeding multiple regions via two distinct evolutionary patterns. In the brain parenchyma, highly proliferative gliomas underwent whole-genome doubling with unstable sub-tetraploid/4N genomes, loss of chromosome 19/*Pten* and PI3K/Akt activation. However, relatively quiescent glioma cells with near-diploid/2N genomes and normal *Pten* were maintained in the subventricular zone (SVZ) stem-cell niche. Akt inhibition by *Rictor*/mTORC2 deletion blocked glioma distant dissemination from the SVZ stem-cell niche. Thus, our study identifies the closest descendants of evolutionarily unobserved localized CAs located in the SVZ, generating highly proliferative and migratory multifocal GBMs at distant locations in an mTORC2/Akt-dependent manner. Further, our study delineates a complex branched pattern of clonal evolution from neural stem cells in the SVZ to highly proliferative and migratory GBM cells in the distant locations of the brain parenchyma.

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Poster

648. Cell Cycle Mechanisms in Neurogenesis II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 648.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Title: Expansion of the radial glia-like stem pool in the hippocampal dentate gyrus is modulated by the chloride importer NKCC1

Authors: K. REICHE[1], S. SRIDHARAN[1], M. CEANGA[1], M. RUDOLPH[1], M. SENFTLEBEN[1], M. GÜNTHER[1], *C. W. SCHMEER[1], K. HOLTHOFF[1], C. A. HÜBNER[2], D. LIE[3], O. W. WITTE[1], S. KEINER[1]
[2]Inst. of Human Genet., [1]Jena Univ. Hosp., Jena, Germany; [3]Friedrich-Alexander Univ., Inst. of Biochem., Erlangen, Germany

Abstract: Throughout life, the process of neurogenesis continues in two specific regions of the adult brain: the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricles. The neurogenic capacity of the hippocampus is dependent on the existence of a population of radial glia-like cells (RGLs) that act as neural stem cells. However, the underlying mechanisms regulating RGL activation throughout life have not been fully elucidated. The inhibitory neurotransmitter GABA, acting via $GABA_A$ receptors, regulates multiple stages of adult neurogenesis including neural progenitor proliferation, migration, neuronal maturation, synaptic integration and survival. The mode of GABA action depends on intracellular chloride levels, which are determined by the differential expression of chloride importers NKCC1 and KCC2. NKCC1 is predominantly expressed in neural precursor cells and drives Cl^- influx. The role of the chloride importer NKCC1 in the activity of RGLs from the dentate gyrus remains unknown. Therefore, we used a novel inducible transgenic mouse model for specific NKCC1 knock-out ($NestinCreER^{T2}/NKCC1^{fl/fl}$/tdTomato mice) in $nestin^+$RGLs. Our data show that NKCC1 knockout strongly promotes the expansion of the RGL neural stem cell population in the adult and aged hippocampal dentate gyrus. Detailed morphometric analysis of RGLs indicated an increase in the cellular complexity as shown by changes in length, width, and surface of the cells in adult and aged mice. Our study shows for the first time that the self-renewal capacity of RGLs in the adult and aged hippocampal dentate gyrus is strongly modulated by the chloride importer NKCC1. Understanding the underlying mechanisms of neural stem cell activation throughout life is important to restitute the stem cell pool and generate new neurons, thereby improving the cognitive function during aging.

Disclosures: **K. Reiche:** None. **S. Sridharan:** None. **M. Ceanga:** None. **M. Rudolph:** None. **M. Senftleben:** None. **M. Günther:** None. **C.W. Schmeer:** None. **K. Holthoff:** None. **C.A. Hübner:** None. **D. Lie:** None. **O.W. Witte:** None. **S. Keiner:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.01/B1

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH 1F31MH11014601

Title: Serotonin receptor mechanism regulating adult neural stem cells in the mouse hippocampus

Authors: *A. J. CROWTHER[1], J. SONG[2]
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Abstract: Antidepressants targeting the serotonin system are commonly ineffective for 40% of patients with unclear causes. Adult hippocampal neurogenesis may be a critical substrate of successful treatment response. Animal models of depression have reduced hippocampal neurogenesis that is reversed by antidepressants. Furthermore, neurogenesis is required for specific behavioral responses to SSRIs in animal models. However, most previous studies employ systemic broadly-acting drugs or complete removal of neurogenesis through genetic approaches or focal irradiation. Circuit and cell-type specific postsynaptic effects of antidepressants are not well understood. We take a circuit-based approach in combination with cell-type specific conditional genetics to investigate serotonin receptor mechanisms controlling two critical stages of neurogenesis, stem cell fate choice and proliferation of neural progenitors. We demonstrate that selective 5-HT1A receptor deletion in adult neural stem cells leads to increased glial differentiation of stem cells, whereas its deletion in neural progenitors leads to increased proliferation. Furthermore, chemogenetic activation of 5HT circuitry leads to increased quiescence of neural stem cells in the dentate gyrus. Our studies establish a novel activity-dependent mechanism by which early hippocampal neurogenesis is regulated by 5-HT.

Disclosures: A.J. Crowther: None. **J. Song:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.02/B2

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH R01 NS094176

Title: Quantification of efficiency for understanding larval zebrafish fine motor control development and modulation

Authors: *S. WAHLSTROM-HELGREN, A. BOWMAN, K. VANPELT, M. A. MASINO
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: During free-swimming, larval zebrafish perform a lateral undulation that translates into fluid motion around the fish to propel it forward. This transformation of lateral movement to forward motion is performed with a given efficiency, which is dependent on the coordination of strength and timing of the muscle groups. Therefore, a quantification of this transformation can be used to assess refinement of fine motor control during development or to determine the effects of perturbations to the locomotor circuitry. Here, we tested the hypothesis that larval locomotion becomes more efficient as development proceeds—less lateral undulation is required to move the same distance because of increased coordination and strength of the muscle groups. In this study, we utilized high-speed video (210 frames per sec) recordings, Ctrax software (an open-source

tracking software), and physics first principles to study how this transformation occurs during development, and how the transformation can be perturbed by modulatory neurotransmitters. Specifically, we quantified and correlated the power produced by the undulation and the power of the forward movement of the fish. As predicted, we found that the power measures became more strongly correlated and the variance was reduced across developmental stages (3 days post-fertilization (dpf) to 7dpf). Previous work in the lab showed that between 3dpf and 4dpf a switch in swimming behavior occurs where swim episodes significantly decreased in duration. Furthermore, blockade of dopamine 4 receptors (D4Rs) can reverse this switch in the 4dpf and older larvae. Therefore, we asked if/how the power measures were altered in the presence of a D4R antagonist when applied to post-switch (5dpf) larvae. We found that the correlation between the power measures increased and the variance was reduced. Interestingly, D4R antagonism increased the efficiency of the transformation; correlation higher and variance lower. In conclusion, we have established a novel method to quantify the efficiency of the free-swimming larval zebrafish locomotor pattern, which can be applied to systematically examine the effects of various modulated states of the locomotor circuitry.

Disclosures: S. Wahlstrom-Helgren: None. **A. Bowman:** None. **K. Vanpelt:** None. **M.A. Masino:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.03/B3

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH R01 NS094176

Title: Motor control of swimming is developmentally refined in larval zebrafish

Authors: *M. A. MASINO, K. VANPELT, A. BOWMAN, S. WAHLSTROM-HELGREN
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Fine motor skills are acquired throughout development. In zebrafish, we expect that the acquisition of fine motor control during larval development is reflected in the swimming locomotor pattern and that this control can be quantified by examining various properties of the locomotor pattern. Previous work from the lab has shown a developmentally-mediated switch in swim episode duration (decrease) and frequency (increase) that occurs in larvae between 3dpf (days post-fertilization) and 4dpf. We hypothesize that other swim properties—i.e. maximum forward velocity, distance traveled per episode, and tail-beat frequency—will also be refined as fine motor control develops. Using high-speed (210 frames per sec) video recordings, we tracked swimming zebrafish larvae with Ctrax (an open source tracking software) across developmental

stages to encompass both the pre- and post-switch states, at 3dpf, 5dpf, and 7dpf. Swim episodes were identified with an in-house MatLab script and the properties of interest measured. The magnitude of all three measures decreased and the variance reduced as the larvae progressed from 3dpf to 7dpf reflecting the development of fine motor control. Our previous work showed that the application of a dopamine 4 receptor (D4R) antagonist to 4dpf larvae (post-switch) reversed the locomotor pattern from frequent, short episodes to infrequent, long episodes. Therefore, to determine the effects of D4R antagonism on the properties of interest we applied the D4R antagonist to 5dpf (post-switch) larvae. Interestingly, we found that all three measures decreased in a manner similar to that of the behavior of the untreated 7dpf larvae. This result was both unexpected and interesting because the blockade of the D4Rs does not simply revert the swimming pattern to a pre-switch state, but instead influences episode duration and episode frequency towards the pre-switch state while the other properties--maximum forward velocity, distance traveled per episode, and tail-beat frequency--become further refined. Future work will focus on understanding the underlying mechanism of dopamine action onto D4Rs to effect these behavioral properties.

Disclosures: **M.A. Masino:** None. **K. Vanpelt:** None. **A. Bowman:** None. **S. Wahlstrom-Helgren:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.04/B4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH

NIAAA

ABMRF

NARSAD

CTSI

Scot-Gentle foundation

Title: IGFR-Akt signaling through primary cilia protects developing neurons from the dendritic degeneration elicited by environmental stress

Authors: ***S. ISHII**[1], S. MOHAMMAD[1], T. SASAKI[1], M. TORII[1,2,3], K. HASHIMOTO-TORII[1,2,3]

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Abstract: GABA mimicry and NMDA antagonistic reagents including alcohol and analgesic agents induce neurodegeneration in the developing brain. The developmental exposure to those agents increases the risks of neurological and psychiatric diseases. Therefore understanding the underlying molecular mechanisms is crucial for developing potential interventions for such acquired neuropsychiatric conditions. Here we show that the lack of primary cilia in the developing cerebral cortex augmented alcohol's effects that reduce/degenerate dendritic arborization through excessive fragmentation of cytoskeletal proteins by activated caspase-3. Consistently, microglial accumulation and activation were enhanced in the cilia-deficient mice exposed to ethanol. In the cilia-deficient cortical neurons, we found reduced activation of IGF receptors, while phosphorylation of S6, a downstream of mTOR signaling, was increased. Notably, the loss of protection of cortical neurons in the lack of primary cilia was rescued by administration of Akt agonist to the alcohol-exposed mice. These results suggest a mechanism of neuroprotection by IGFR-Akt signaling that requires the primary cilia. Therefore enhancing such cilia-mediated intrinsic protective mechanisms may become a potential intervention for acquired brain injury during brain development and the associated neurobehavior problems.

Disclosures: S. Ishii: None. **S. Mohammad:** None. **T. Sasaki:** None. **M. Torii:** None. **K. Hashimoto-Torii:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.05/B5

Topic: A.01. Neurogenesis and Gliogenesis

Support: University Grants Commission (India) Grant

TIFR-DAE Intramural funds

Wellcome Trust-Department of Biotechnology India Alliance Early Career Fellowship Grant IAE/11/1/500402

Department of Biotechnology (India) Grant BT/PR8681/MED/30/1028/2013

Title: Multiple functions of Ldb1 in dorsal telencephalic development

Authors: *V. J. KINARE[1], H. PADMANABHAN[2,3,4], G. GODBOLE[2], Z. KHATRI[2], U. MAHESHWARI[2], B. MURALIDHARAN[2], S. P. TOLE[2]
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Abstract: Ldb1 (LIM Domain Binding Protein 1) is a transcriptional cofactor which interacts with various LIM-HD, Lmo, Otx and bHLH proteins, many of which are known regulators of telencephalic development (Mangale et al., 2008; Zhao et al., 1999; Johanssen et al., 2013) . In order to study role of Ldb1 in regulating telencephalon morphogenesis and to circumvent early embryonic lethality (Mukhopadhyay et al., 2003), we used a floxed *Ldb1* line in conjunction with different Cre drivers known to act during early telencephalic development.
Surprisingly, we found that these drivers recombine the floxed *Ldb1* locus with different degrees of efficiency in the embryonic mouse dorsal telencephalon. While *Foxg1Cre* deletes *Ldb1* from the entire dorsal and ventral telencephalon by embryonic day (E) 12.5, *Emx1Cre*, which acts only in the dorsal telencephalon, displays efficient floxing medially, and less efficient floxing laterally by this stage. These differential effects are specific to the floxed *Ldb1* locus, since a standard floxed *Ai9* reporter line displays efficient floxing appropriate for each Cre line by E12.5. With time, however, the floxing efficiency at the Ldb1 locus appears to improve, such that by E15.5, there is no medio-lateral difference in the case of *Emx1Cre*. Therefore, our results suggest caution in interpreting the effects of conditional loss of Ldb1, since the actual recombination of the gene may not have occurred at the expected time point as assessed by the floxing of reporter lines.
Loss of Ldb1 using *Foxg1Cre* recapitulates many of the phenotypes seen in Lhx2 loss of function brains, while also exhibiting some unexpected and novel phenotypes. Loss of Ldb1 using *Emx1Cre* causes efficient recombination in the hippocampal primordium, and profoundly disrupts hippocampal development. We were able to rescue the hippocampal defects using a chimeric *Ldb1-Lhx2* construct, demonstrating that an Ldb1-Lhx2 complex is the active complex critical for the regulation of hippocampal specification and neurogenesis. Therefore, the functional partner for Ldb1 in hippocampal development appears to be Lhx2.

Disclosures: V.J. Kinare: None. **H. Padmanabhan:** None. **G. Godbole:** None. **Z. Khatri:** None. **U. Maheshwari:** None. **B. Muralidharan:** None. **S.P. Tole:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.06/B6

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI 24800088

FIRST from JSPS

WPI from MEXT

15H04268 from MEXT

15K14337 from MEXT

15H01304 from MEXT

Title: Hypothalamic Ptf1a is required for sexual differentiation of the brain and behavior

Authors: *T. FUJIYAMA[1,2], S. MIYASHITA[2], Y. TSUNEOKA[3], M. NAGAOKA[2], M. KAKIZAKI[1], S. KANNO[1], Y. ISHIKAWA[1], Y. KAWAGUCHI[4], Y. YANAGAWA[5], M. A. MAGNUSON[6], Y.-I. NABESHIMA[7], M. YANAGISAWA[1], H. FUNATO[3], M. HOSHINO[2]
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Abstract: The brain has sexual differences in structure and function, which are determined during the critical period (from embryonic day 16 to P8 in mice) by the sex steroid hormonal milieu. However, it remains unknown how the developing brain acquires the ability to respond to the gonadal hormones before the critical period. *Pancreas transcription factor 1a (Ptf1a)* is expressed in the developing brain and known to be required for the proper maturation of the cerebellum, brain stem and spinal cord. Although the preoptic area and ventral diencephalon are only regions where *Ptf1a* is expressed in the developing forebrain, the role of *Ptf1a* in these regions is largely unknown. Here we report that hypothalamus-specific *Ptf1a*-deficient (cKO) mice (*Nkx2.1-Cre; Ptf1a-flox*) exhibited abnormalities in sexually-biased behaviors such as mating, aggression and parenting. *Ptf1a* cKO mice also showed maldevelopment of gonadal tissues in both sexes. Histological examination revealed that sexual differences in hypothalamic gene expressions of *Ptf1a* cKO mice were different from those of control mice. We did not detect any overt changes in the hypothalamic structures in *Ptf1a* cKO mice nor an increased cell death in the hypothalamus of *Ptf1a*-null mice. Next, we performed microarray analysis using FACS-sorted cells expressing *Ptf1a*-YFP from E14 brains, which showed a significant decrease in *Kiss1* gene expression. We confirmed a decreased *Kiss1* mRNA in adult *Ptf1a* cKO mice using quantitative PCR. In addition, *Kiss1*-positive cell numbers in the anteroventral periventricular (AVPV) and arcuate nucleus (ARN) were markedly decreased in both sexes. Since the *Kiss1* gene encodes kisspeptin that is required for sexual maturation and directly regulates the release of gonadotropin releasing hormone (GnRH) from the anterior pituitary, the current results suggest that hypothalamic *Ptf1a* is required for sexual differentiation of the brain and gonadal tissues via proper kisspeptin expression.

Disclosures: **T. Fujiyama:** None. **S. Miyashita:** None. **Y. Tsuneoka:** None. **M. Nagaoka:** None. **M. Kakizaki:** None. **S. Kanno:** None. **Y. Ishikawa:** None. **Y. Kawaguchi:** None. **Y.**

Yanagawa: None. **M.A. Magnuson:** None. **Y. Nabeshima:** None. **M. Yanagisawa:** None. **H. Funato:** None. **M. Hoshino:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.07/B7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant K01MH109747

NIH Grant R01NS035129

Howard Hughes Medical Institute

Title: Cell-type-specific alternative splicing controls cerebral cortex development

Authors: *X. ZHANG[1], X. WU[2], M. CHEN[1], J. FAN[3], D. BLACK[4], D. V. KHARCHENKO[3], P. A. SHARP[2], C. A. WALSH[5]
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Abstract: Alternative splicing is widespread in the brain but its role in regulating neural progenitor cell (NPC) fate remained an open question. Using single cell RNA-Seq and mouse reporter lines, we studied NPCs and neurons purified from the developing mouse and human cerebral cortices, and uncovered hundreds of alternatively spliced exons that preferentially affect cytoskeletal proteins. We demonstrated that Ptbp1 and Rbfox proteins antagonistically regulate the NPC-to-neuron transition by regulating a group of neuron-specific exons. While Ptbp1 maintains apical progenitor lamination through suppressing a poison exon of *Flna* in NPCs, Rbfox proteins promote neuronal differentiation by switching Ninein from a centrosomal splice form in NPCs to a non-centrosomal isoform in neurons. We further identified a deep intronic human mutation within a PTBP1 binding site that disrupts normal skipping of the FLNA poison exon in NPCs and causes a brain-specific malformation. This study indicates that cell-type-specific alternative splicing controls neurogenesis in the developing cerebral cortex.

Disclosures: X. Zhang: None. **X. Wu:** None. **M. Chen:** None. **J. Fan:** None. **D. Black:** None. **D.V. Kharchenko:** None. **P.A. Sharp:** None. **C.A. Walsh:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.08/B8

Topic: A.01. Neurogenesis and Gliogenesis

Title: Thalamic and behavioral repercussions following cortex-specific deletion of Emx2

Authors: S. I. AKHIDENOR[1], N. A. CASTRO BORJAS[1], A. K. SWEDZINSKI[1], K. M. HIXSON[1], A. MACGREGOR[1], A. B. ZEMBRZYCKI[2], *A. M. STOCKER[1]
[1]Biosci., Minnesota State Univ. Moorhead, Moorhead, MN; [2]SBP/GSK Ctr. for Translational Neurosci., Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: The mammalian cortex is comprised of several primary sensory areas, which receive information from the periphery relayed through the appropriate sensory specific thalamic nuclei. The developmental process through which the neocortex is subdivided into distinct functional areas is called area patterning. Studies investigating intrinsic area patterning mechanisms have shown that transcription factors are expressed in different mediolateral and rostrocaudal gradients by cortical progenitors during early corticogenesis, which specify positional/areal identities. Previous research exploring cortex-specific deletion of Pax6 revealed top-down plasticity in the thalamus. More specifically, a genetic driven reduction of the primary somatosensory area subsequently caused a reduction in the somatosensory thalamic nucleus (ventral posterior). Previous research has shown that a cortex-specific deletion of Emx2 causes a decrease in posterior area size, particularly the visual areas. To determine if top-down plasticity is present in the visual system following area patterning changes, we examined the size of specific thalamic nuclei following cortex-specific Emx2 deletion (mediated by Emx1 driven Cre-recombinase). We observed no changes in dorsal lateral geniculate size (the visual thalamic nucleus) in Emx2 mutants. In contrast, we observed a significant reduction in the size of the reticular thalamic nucleus. However, this reduction was not apparent until the end of the critical period. We also observed behavioral changes that mirrored the timeline of the anatomic changes in the reticular thalamic nucleus. These results indicate top-down plasticity does occur in the visual system, but via mechanisms distinct from those found in the somatosensory system.

Disclosures: S.I. Akhidenor: None. **N.A. Castro Borjas:** None. **A.K. Swedzinski:** None. **K.M. Hixson:** None. **A. Macgregor:** None. **A.B. Zembrzycki:** None. **A.M. Stocker:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.09/B9

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Helse SørØst 2013022

Title: Postmitotic subdivision of the contralateral medial vestibulospinal tract by specific expression of transcription factors

Authors: *A. LUNDE[1], B. W. OKATY[2], S. M. DYMECKI[3], J. C. GLOVER[1]
[1]Univ. of Oslo, Oslo, Norway; [2]Genet., [3]Harvard Med. Sch., Boston, MA

Abstract: The vestibulospinal system is a collection of brainstem to spinal cord projection neurons residing in the vestibular nuclei, and helps animals ranging from agnathans to humans to maintain proper balance and posture. These neurons can be classified into three distinct groups according to their projection pattern and rhombomeric origin. Fate mapping has demonstrated that the ipsilateral lateral vestibulospinal tract (LVST) group derives from rhombomere (r)4, the ipsilateral medial vestibulospinal tract (iMVST) derives from r6, and the contralateral medial vestibulospinal tract (cMVST) group derives from r5 and part of r4 (Di Bonito et al., 2015; Diaz, Puelles, Marin, & Glover, 1998).
To investigate the combinatorial pattern of rhombomeric origin and downstream transcription factor expression in the cMVST neurons, we combined retrograde fluorescent tracing with immunohistochemistry in wild type and r4-Hoxb1-YFP (r4 lineage specific) mouse embryos. We found that r4-derived cMVST neurons express Lbx1 post-mitotically, while the r5-derived component of cMVST neurons is void of Lbx1. Preliminary data suggests that Evx2 has the opposite expression pattern, with r4-derived cMVST neurons being Evx2-negative and r5-derived cMVST neurons being Evx2-positive. Several other transcription factors appear to be quantitatively modulated by rhombomeric origin as assessed by immunostaining intensity.
Thus, the cMVST is subdivided post-mitotically into different transcription factor-specific domains according to rhombomeric origin, suggesting functional subdivisions in the control of neck musculature by the vestibulospinal system.
Di Bonito, M., Boulland, J. L., Krezel, W., Setti, E., Studer, M., & Glover, J. C. (2015). Loss of Projections, Functional Compensation, and Residual Deficits in the Mammalian Vestibulospinal System of Hoxb1-Deficient Mice. *eNeuro, 2*(6). doi:10.1523/eneuro.0096-15.2015
Diaz, C., Puelles, L., Marin, F., & Glover, J. C. (1998). The relationship between rhombomeres and vestibular neuron populations as assessed in quail-chicken chimeras. *Dev Biol, 202*(1), 14-28. doi:10.1006/dbio.1998.8986

Disclosures: A. Lunde: None. **B.W. Okaty:** None. **S.M. Dymecki:** None. **J.C. Glover:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.10/B10

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: FRM grant DEQ20160334891

AFM Grant 18564

Title: Regression of the intrinsic activation properties of Renshaw cells during the early phase of the spinal cord network development

Authors: *P. LEGENDRE[1], J. BOERI[1], H. LE CORRONC[1], B. LE BRAS[1], C. MOUFFLE[1], J. MANGIN[1], P. BRANCHEREAU[2], A. CZARNECKI[1]
[1]INSERM U1130/CNRS UMR 8246, UPMC UM CR18,, Paris, France; [2]Univ. Bordeaux & CNRS - INCIA UMR 5287, Pessac Cedex, France

Abstract: Context: As in many central nervous system areas, the embryonic spinal cord (SC) generates spontaneous rhythmic synchronized neural activity (SNA). SNA is essential for the development of neuronal networks. In the mouse embryonic SC, SNA emerges at the onset of synaptogenesis (E12.5 to E14.5) and then disappears when the first locomotor networks become functional (after E15.5). SNA is characterized by the periodic occurrence of giant depolarizing potentials (GDPs) in motoneurons (MNs), mainly due to the massive release of GABA. Among the several SC GABAergic interneurons (INs), the V1 INs are one of the first INs projecting onto MNs at the onset of SNA. But how the intrinsic activation properties of these INs develop and consequently control GDPs remain open questions. Aim: To address this issue, we analyzed the development of the intrinsic activation properties of V1 INs and of MNs between E12.5-E14.5. Methods: MNs and V1 INs recorded using whole-cell patch-clamp in the SC open-book preparation. Results: At E12.5, V1 INs identified by FoxD3 and calbindin (Renshaw cells), displayed various firing patterns. Cluster analysis revealed that this heterogeneity reflects different regimes of intrinsic activation properties that can be classified as single-spiking, repetitive-spiking or sodium-dependent plateau potential regime. To the contrary, MNs displayed only single-spiking or repetitive-spiking regimes. We discovered that regimes of intrinsic activation properties of V1 INs and MNs depend on the ratios of the persistent sodium current (INaP) versus the delayed voltage-dependent potassium currents (IKdr). Blockade of INaP with riluzole convert plateau potential or repetitive-spiking into single-spiking cell while reduction of IKdr convert single-spiking into plateau potential or sustained-firing regimes. MNs intrinsic excitability develops in a classical way between E12.5 and E14.5, with an increase in the proportion of MNs firing repetitively at E14.5. To the contrary, V1 INs lose their ability to generate repetitive-spiking or plateau potential at E14.5 related to a decrease in the gNaP/gKdr

ratio. This regression in V1 INs intrinsic activation properties is transitory since these INs are able to fire repetitively at later developmental stages.

Disclosures: **P. Legendre:** None. **J. Boeri:** None. **H. Le Corronc:** None. **B. Le Bras:** None. **C. Mouffle:** None. **J. Mangin:** None. **P. Branchereau:** None. **A. Czarnecki:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.11/B11

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant MH113257

Title: MacBrainResource: Collection of slides and tissues enables study of non-human primate development and architecture

Authors: *L. D. SELEMON, A. DUQUE
Dept Neurosci., Yale Univ. Sch. Med., New Haven, CT

Abstract: A macaque brain tissue resource (MacBrainResource), designed for the study of developmental neurobiology, neurocytology and neuroanatomy is now available to the neuroscience community at large. The mission of this newly NIH-supported resource is to facilitate access to non-human primate brain slides, fixed and frozen tissue and EM blocks produced by decades of study in the laboratories of Drs. Pasko Rakic and Patricia S. Goldman-Rakic at Yale University. MacBrainResource includes an extensive collection of ^{3}H-thymidine labeled brain slides for the study of neurogenesis (Set 1). To generate this collection, ^{3}H-thymidine was injected into pregnant rhesus monkeys for uptake into fetal brains ranging in age from near conception (E29) to the end of gestation (E165), and into postnatal monkeys as well. Survival times varied from 1 hour to days, months, and years so that the place and time of origin, kinetics of proliferation and rate of migration of various classes of neurons and their settling patterns can be studied. Serial sections throughout the entire brain were cut generally at 20 μm thickness, and every 20th section was developed autoradiographically and Nissl counterstained. Only limited regions of the brain have been studied for the time of neuron origin, leaving the vast majority of cell populations available for analysis and publication. Unstained, intermediate sections were collected as well; these could be utilized for developmental studies via the application of new methods. Slides may be accessed on site at Yale or remotely via electronic images uploaded to the website, MacBrainResource.org, by request. Other available material includes autoradiographically labeled slides from brains with ^{3}H-amino acids injections for anterograde tract-tracing (Set 2), slides from animals with prenatal or postnatal lesions (Set 3), slides prepared for stereological analysis from adult monkeys that had been fetally irradiated and

corresponding control sham-irradiated and non-irradiated animals (Set 4), and EM blocks of multiple brain regions at all ages of development (Set 5). MacBrainResource affords neuroscientists worldwide a means to address questions about non-human primate development and structure that are pertinent to contemporary issues in basic neurobiology and human disease. Moreover, access to archived brain materials will enable researchers to perform *de novo* non-human primate research without the need to sacrifice any additional animals.

Disclosures: L.D. Selemon: None. **A. Duque:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.12/B12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSERC M3

Title: Small molecules instruct rod photoreceptor progenitor fate or permit cone photoreceptor progenitor fate from mammalian retinal stem cells

Authors: *J. J. BELAIR-HICKEY[1], S. KHALILI[1], B. G. BALLIOS[2], K. N. GRISÉ[1], B. L. K. COLES[1], V. WALLACE[3], G. BERNIER[4], D. VAN DER KOOY[1]
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Abstract: The adult mammalian eye contains a rare population of quiescent retinal stem cells (RSCs) within the pigmented ciliary retinal margin having the ability to self-renew and give rise to all cell types of the retina *in vitro*. When plated at a clonal density a single RSC will divide to produce a free-floating sphere colony of ~3000-5000 cells, of which the majority are either retinal pigmented epithelial (RPE) progenitors or non-pigmented neural retinal (NR) progenitors. Here we report the isolation of lineage restricted photoreceptor progenitor cells derived from murine RSCs, allowing for the production of pure populations of photoreceptors *in vitro*. When RSC-derived NR progenitors were plated at a single-cell per-well density and exposed to COCO (a secreted multifunctional inhibitor of BMP / Wnt / TGFβ signalling pathways) for 45 days, nearly all of the clones were 100% positive for cone-arrestin and s-opsin (markers of mature post-mitotic s-cone photoreceptors). Furthermore, COCO needed to be present throughout the entire differentiation period to induce cone photoreceptor fate. These data suggest that the inhibition of these three major signalling pathways is acting to cause NR progenitors to default towards an s-cone photoreceptor fate, a concept that has been proposed for cone developmental *in vivo*. In contrast, when single non-pigmented NR progenitors were exposed to taurine +

retinoic acid (T/RA) for 40 days, all clones contained 100% rhodopsin positive cells (a marker of post-mitotic mature rod photoreceptors). Unlike COCO, however, T/RA does not need to be present throughout the entire differentiation period, and can be removed during later time-points while still producing enriched rod photoreceptor clones. This indicates that, unlike cone photoreceptor development, T/RA is acting in an instructive manner to bias NR progenitors towards a rod lineage-restricted cell fate. In both cases, the size and survival of clones was no different compared to NR progenitors exposed to a pan-retinal differentiation condition in 1% FBS, arguing against COCO or T/RA having a selective survival effect on photoreceptor lineage restricted progenitor cells. In addition to murine eyes, RSCs can also be isolated from both human donor eyes and human pluripotent stem cells. The ability to derive cone or rod lineage-restricted progenitors from these sources provides potentially inexhaustible sources of rods and cones for therapeutic applications, as well as a developmental system to study the molecular identity of photoreceptor lineage-restricted progenitors in a human context.

Disclosures: J.J. Belair-Hickey: None. **S. Khalili:** None. **B.G. Ballios:** None. **K.N. Grisé:** None. **B.L.K. Coles:** None. **V. Wallace:** None. **G. Bernier:** None. **D. van der Kooy:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.13/B13

Topic: A.01. Neurogenesis and Gliogenesis

Support: YCP FDC Summer Research Program

Title: Characterization of transcription factor expression during retinal development in gallus gallus

Authors: B. KABLE[1], *S. A. GEORGI[2]
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Abstract: During retinal development, a group of multipotent progenitor cells give rise to six types of neurons and one type of glia in a conserved order, with ganglion cells being produced first, and Müller glia last. While numerous transcription factors that control this process have been identified and characterized, the details by which these genes regulate the process of cellular differentiation is still unclear. It is likely that many of these transcription factors represent only the first steps of the genetic cascades of differentiation, and that there are additional transcription factors that play a role in activating or repressing the genes necessary to convert a retinal progenitor cell into a functional neuron or glial cell. In previous studies (Georgi and Reh 2010) we performed a conditional knockout (CKO) of Dicer, an enzyme required for microRNA biogenesis, and observed that retinal progenitor cells did not produce late cell types.

This suggested they were arrested in an early competence state, and to determine genetic changes that might underlie this phenotype we performed a microarray of Dicer CKO retina (La Torre et al. 2013). We hypothesize that those genes that decreased on the microarray are involved in the generation of late cell types. Interestingly, on this list were numerous transcription factors whose expression and function in the retina has not yet been characterized. The aim of this study is to provide initial characterization of the expression of these unstudied transcription factors during chicken retinal development using qPCR and immunohistochemistry. Our data support our hypothesis that these transcription factors play a role in late retinal development, and provide a foundation for future studies into the specific developmental function of these genes.

Disclosures: B. Kable: None. **S.A. Georgi:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.14/B14

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R01EY024982

Title: Comparative analysis of cone and horizontal cell restricted progenitors and multipotent progenitors in the vertebrate retina

Authors: *D. F. BUENAVENTURA[1,2], M. GHINIA[1], M. EMERSON[1]
[1]City Col. of New York, New York, NY; [2]Biol., CUNY Grad. Ctr., New York, NY

Abstract: Every cell type in the vertebrate retina is derived from multipotent retinal progenitor cells (RPCs). Current evidence suggests that some RPCs are molecularly restricted to produce only certain cell types. Little is known about how many types of restricted RPC populations exist or what distinguishes them molecularly from multipotent RPCs. The ThrbCRM1 regulatory element is activated by OC1 and OTX2 and drives reporter expression in one type of restricted RPCs that preferentially generate cones and horizontal cells. RNAseq of the ThrbCRM1+ cell population shows an upregulation of cone and HC-specific transcripts and downregulation of traditional multipotent progenitor markers. Further characterization of the ThrbCRM1+ premitotic subpopulation in the chicken retina at E5 suggests that OC1/OTX2+ progenitors downregulate multipotent markers VSX2/LHX2/PAX6 at different rates during the restriction process and become spatially segregated from the remaining multipotent progenitor population. At E6, our analysis indicates that a subset of OTX2/OC1+ RPCs remain apically and begin to upregulate a photoreceptor-specific marker, while another subset downregulate OTX2+ but maintain OC1 expression and migrate to the basal retina for another mitotic event. Therefore, our

data suggests that cone and HC progenitors at E5/E6 exhibit a different molecular signature and behavior than LHX2/VSX2/PAX6+ proliferating multipotent progenitors.

Disclosures: D.F. Buenaventura: None. **M. Ghinia:** None. **M. Emerson:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.15/B15

Topic: B.12. Glial Mechanisms

Support: CIHR grant to ESR

NSERC Banting Fellowship to MRVH

Title: D-serine modulation of glutamatergic transmission disrupts retinotectal input convergence in the developing visual system

Authors: *M. VAN HORN, E. S. RUTHAZER
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Abstract: N-methyl-D-aspartate receptor (NMDAR) activation is essential for establishing and maintaining precise neural circuit refinement. The gliotransmitter D-serine is a co-agonist for NMDARs and modulates synaptic transmission and plasticity mediated by this receptor. Here we investigated the role D-serine plays in modulating synaptic transmission and axonal remodeling in the developing visual system of the Xenopus tadpole. We find that D-serine is an endogenous co-agonist of the NMDAR that is normally present below saturating levels and show that glutamate receptor activation can evoke endogenous D-serine release, which promotes glutamatergic synapse maturation and stabilizes axonal structural and functional inputs. Here, to test the functional consequence of chronic enhancement of NMDAR currents by exogenous D-serine, we performed whole-cell recordings in vivo while presenting patterned visual receptive field mapping stimuli in control animals and in animals raised in D-serine for 48 h. Each location in a 7 by 7 grid of visual subfields was illuminated at random to map out the synaptic currents evoked by subfield illumination. Responses evoked after the illumination of the light (ON) as well as the extinction of the light (OFF) were analyzed. Consistent with previous studies, we found that OFF responses were typically larger than corresponding ON responses in control animals, as indicated by the mean OFF/ON peak response ratio of 1.74 ± 0.27. In contrast, ON and OFF responses from cells recorded from animals raised in D-serine were more closely matched (OFF/ON ratio: 0.83 ± 0.08). Interestingly, a comparison of the sum of responses across all subfields revealed that the overall response is greater in D-serine animals and a comparison of the size of the receptive field shows that the ON response is significantly larger in the D-serine

animals. Taken together these results suggest that D-serine exposure promotes a non-specific strengthening of retinal ganglion inputs leading to a more divergent receptive field map. Overall, these findings positively implicate NMDAR-mediated neurotransmission in developmental synapse maturation and the stabilization of axonal inputs and reveal a potential role for D-serine as an endogenous modulator of neural circuit refinement.

Disclosures: M. Van Horn: None. **E.S. Ruthazer:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.16/B16

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF Grant 1257895

NIH Grant 1R15HD077624-01

Title: The role of purinergic receptors in early neural calcium activity

Authors: *S. BRACERO, L. G. YI, S. PAUDEL, M. S. SAHA
The Col. of William and Mary, Williamsburg, VA

Abstract: Although calcium plays an essential role as a signaling molecule during neural development, very little is known about what triggers the observed dramatic fluctuations. The purinergic receptors are a large family of highly conserved proteins that bind purines such as ATP and have been implicated as mediators of calcium activity and cell proliferation during early neural development. Here we have cloned members of the purinergic receptor family in an attempt to determine if they are mediating the widespread calcium activity that occurs throughout gastrula and neurula stages of development. In particular, the Y family G protein-coupled purinoreceptor P2RY11 was cloned and characterized in *Xenopus laevis* during embryonic development. Expression of this receptor was observed starting at the early neurula stage in the posterior tip, and in the tailbud of early tailbud stage embryos, which has never before been observed. Expression was also observed in the developing notochord, which is consistent with previous reports on the expression of P2RY11. Due to its temporally and spatially restricted expression patterns, the role of P2RY11 in tailbud regeneration was investigated through amputation experiments. P2RY11 was not expressed in response to tail amputation. Given these results, P2RY11 is likely involved in the formation of the tailbud during development, but is not responsible for its proliferative and regenerative abilities. However, calcium imaging of tailbud cells in the presence and absence of NF-157, a P2RY11 antagonist, revealed that P2RY11 may mediate high frequency, low amplitude calcium spiking and that

P2RY11 may be involved in early neural patterning. Here we report the expression patterns of P2RY11 and other purinergic family members in neural development.

Disclosures: S. Bracero: None. **L.G. Yi:** None. **S. Paudel:** None. **M.S. Saha:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.17/B17

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Children's Hospital of Wisconsin Research Institute

Title: Effects of neonatal hyperoxia on the critical period of postnatal development of neurochemical expressions in brain stem respiratory-related nuclei in the rat

Authors: L. MU[1], T. MICHALKIEWICZ[2], G. G. KONDURI[2], M. HODGES[3], *M. T. WONG-RILEY[4]
[1]Cell Biology, Neurobio. and Anat., [2]Pediatrics, [3]Physiol., [4]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: We have identified a critical period of postnatal respiratory development in the rat at postnatal days P12-13, when inhibitory influence dominates and when the response to hypoxia is at its weakest. This critical period has significant implications for Sudden Infant Death Syndrome (SIDS), the cause of which remains unclear. One of the known risk factors for SIDS is prematurity. A common intervention used in premature infants is exposure to hyperoxia, which, if prolonged, can alter the ventilatory response to hypoxia and induce sustained inhibition of lung alveolar growth and pulmonary remodeling. The goal of the present study was to determine if neonatal hyperoxia causes neurochemical changes in brain stem respiratory-related nuclei. Sprague-Dawley rats of both sexes were exposed to 90% oxygen from the day of birth (P0) until P10. They were then euthanized at 4 time points: P10 (immediately after hyperoxia and before the critical period), P12 (during the critical period), P14 (immediately after the critical period), and P17 (a week after the cessation of hyperoxia). Control animals were exposed only to room air. Brain stems of all animals were processed for cytochrome oxidase histochemistry and neurochemical immunohistochemistry followed by optical densitometry of reaction product within single neurons of respiratory-related hypoglossal nucleus, pre-Bötzinger nucleus, the ventrolateral subnucleus of nucleus tractus solitarius, and brain stem raphé nuclei, as well as in the non-respiratory cuneate nucleus (CN). In agreement with our previous findings, levels of cytochrome oxidase, brain-derived neurotrophic factor (BDNF), TrkB (high-affinity receptor of BDNF), and several proteins governing serotonergic functions (5-HT_{1A} and $_{2A}$ receptors, 5-HT synthesizing enzyme tryptophan hydroxylase [TPH], and serotonin transporter [SERT]) all fell

during the critical period (P12) in control animals. However, in hyperoxic animals, the levels of these neurochemicals fell at P14 and not at P12. Thus, neonatal hyperoxia appears to delay but not eliminate the critical period of postnatal development in multiple brain stem respiratory-related nuclei, but not in non-respiratory cuneate nucleus of the brain stem. (Supported by Children's Hospital of Wisconsin Research Institute)

Disclosures: L. Mu: None. **T. Michalkiewicz:** None. **G.G. Konduri:** None. **M. Hodges:** None. **M.T. Wong-Riley:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.18/B18

Topic: F.05. Neuroimmunology

Support: LE&RN Postdoctoral Fellowship

NIH AG034113

NIH NS096967

National MS Society

Title: Meningeal lymphatics control brain immune surveillance and play key role during neuroinflammation

Authors: *A. LOUVEAU[1], J. HERZ[2], M. ALME[2], G. HEROD[2], J. SETLIFF[2], K. VIAR[2], S. DA MESQUITA[2], I. SMIRNOV[4], R. CAO[2], S. HU[2], G. OLIVER[5], J. KIPNIS[3]
[1]Ctr. For Brain Immunol. and Glia, Charlottesville, VA; [3]Neurosci., [2]Univ. of Virginia, Charlottesville, VA; [4]Univ. of Charlottesville, Charlottesville, VA; [5]Northwestern Univ., Chicago, IL

Abstract: The central nervous system (CNS) is considered an immune privilege organ, primarily due its lack of lymphatic system. Contrary to the parenchyma, the meninges have recently been shown to harbor a conventional and functional lymphatic system capable of draining cerebrospinal fluid (CSF). Here we demonstrate that the meningeal lymphatic system extends initial buttons to the sub-arachnoid space (SAS) enabling circulation of macromolecules and immune cells from the CSF/meningeal compartments into the cervical lymph nodes. Using both photoconversion approach and exogenously labeled immune cells, our results show that the CCR7-CCL21 pathway is the primary driver of cell drainage from the CSF/meningeal compartments. Furthermore, we demonstrate, using genetic, surgical and chemical approaches that the meningeal lymphatic route is the main route for immune cells circulation. We could not

confirm the role of nasal route in immune cell recirculation, as has been previously suggested. The meningeal lymphatics have a unique transcriptomic profile preventing them to morphologically respond to local neuroinflammation. Nevertheless, their ablation results in delayed and ameliorated clinical symptoms in an animal model of multiple sclerosis (experimental autoimmune encephalomyelitis; EAE). Interestingly, analysis of T cells in mice with ablated lymphatic suggests a failure of activation and acquisition of proper encephalitogenic program to reach the CNS and cause pathology. These results suggest that meningeal lymphatic vasculature plays a central role in the generation and maintenance of the immune responses towards the CNS-derived antigens, notably by modulating the licensing of peripheral encephalitogenic T cells in the cervical lymph nodes. The meningeal lymphatic vasculature might therefore represent a therapeutic target for modulation of the immune responses directed towards the CNS.

Disclosures: A. Louveau: None. **J. Herz:** None. **M. Alme:** None. **G. Herod:** None. **J. Setliff:** None. **K. Viar:** None. **S. Da Mesquita:** None. **I. Smirnov:** None. **R. Cao:** None. **S. Hu:** None. **G. Oliver:** None. **J. Kipnis:** None.

Poster

649. Adult and Developmental Neurogenesis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 649.19/B19

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH 5R03AG051205

Title: Suppression of BIM upregulation and apoptotic death by chronic depolarization of NGF-deprived sympathetic neurons

Authors: A. A. ALSHAMRANI, *J. L. FRANKLIN
Univ. of Georgia, Athens, GA

Abstract: Survival of developing sympathetic neurons is determined by the availability of nerve growth factor (NGF) at the time of innervation of their target organs. NGF-deprived sympathetic neurons in cell culture die by apoptosis within 48-72 h after deprivation, a hallmark of which is the upregulation of BH3-only pro-apoptotic proteins. Chronic depolarization induced by elevated potassium concentration promotes the survival of these cells and that of many other types of neurons in culture and is thought to be a model for the role of electrical activity in promoting neuronal survival during the development of the nervous system. Suppression of apoptosis by chronic depolarization is mediated by a sustained rise of cytoplasmic free Ca_2^+ concentration. Little is known about how this Ca_2^+ increase blocks apoptotic death. Here we report, that in NGF-deprived sympathetic neurons from mouse superior cervical ganglia (SCG), incrementally

increasing K^+ concentrations induced a concentration-dependent enhancement of survival, with 40 mM as the optimal survival-promoting concentration. Both NGF and 40 mM K^+ rescued NGF-deprived SCG neurons over the same time course, suggesting that they may activate or inhibit the same survival or apoptotic pathways, respectively. Immunoblot experiments revealed that, unlike NGF-deprived neurons, chronically depolarizing these neurons with 40 mM K^+ for 12, 24, 48 h caused a complete suppression of the upregulation of the BH3-only pro-apoptotic protein BIM but not other BH3-only proteins. We are investigating whether suppression of BIM upregulation is a major mechanism by which chronic depolarization promotes survival of sympathetic neurons in culture.

Disclosures: A.A. Alshamrani: None. **J.L. Franklin:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 650.01/B20

Topic: A.02. Postnatal Neurogenesis

Support: NSERC Discovery Grant

Title: Adult neurogenesis in the nucleus accumbens of the rat

Authors: *J. S. SNYDER[1], J. YANG[1], D. R. SEIB[2]
[1]Dept. of Psychology, [2]Dept. of Psycholgy - Snyder Lab., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Adult neurogenesis is well-characterized in the hippocampus and subventricular zone-olfactory bulb. Despite numerous reports, the idea of widespread adult neurogenesis remains controversial. The striatum is one region where neurogenesis has been identified, but the magnitude and temporal characteristics of neuron addition has not been studied in detail. Here, we characterized the phenotype and survival timecourse of adult-born neurons in the nucleus accumbens, a part of the ventral striatum involved in reward and reinforcement-related behaviors. Young adult male and female rats (8 weeks old) were treated with the BrdU to label newborn cells and then brains were collected 1, 2, 4, 8 or 16 weeks later. BrdU+ cells were quantified in both the core and shell regions of the nucleus accumbens, and were examined immunohistochemically for calbindin and calretinin expression, two markers of GABAergic interneuron populations. The total number of BrdU+ cells was greatest at 1 week post-injection and steadily declined thereafter. No BrdU+ cells showed co-labelling for calbindin but approximately 2-3% expressed calretinin at the 4 and 8 week time points. Few BrdU+calretinin+ neurons remained at 16 weeks, possibly because neurons have died, matured into a different GABAergic neuron phenotype, or migrated elsewhere. In follow up experiments we are

examining whether accumbens neurogenesis can be increased by exercise, which robustly increases adult neurogenesis in the hippocampus, and whether newborn accumbens neurons derive from a GFAP+ precursor (likely in the subventricular zone), using GFAP-TK rats. Collectively, our findings suggest that adult neurogenesis is more widespread than is generally appreciated. Specifically, our data identify adult neurogenesis as a novel form of plasticity in the nucleus accumbens that may contribute to reward and reinforcement-related behaviors, many of which are disrupted in psychiatric disorders.

Disclosures: **J.S. Snyder:** None. **J. Yang:** None. **D.R. Seib:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 650.02/B21

Topic: A.02. Postnatal Neurogenesis

Support: Grant-in-Aid for Science Research A (26250003)

Grant-in-Aid for Science Research on Innovative Areas "Mental Time" (25119004)

Title: Developmental formation of perineuronal nets in the mouse hippocampal CA2 area

Authors: *A. NOGUCHI[1], N. MATSUMOTO[1], H. TAMURA[2], Y. IKEGAYA[1]
[1]The Univ. of Tokyo, Tokyo, Japan; [2]L-StaR, Hoshi Univ., Tokyo, Japan

Abstract: Perineuronal nets (PNNs) are extracellular macromolecules that consist of several components, including chondroitin sulfate proteoglycans, hyaluronan, and tenascin-R. PNNs exist mostly around inhibitory interneurons, such as parvalbumin-positive interneurons, and are also present around excitatory neurons in several other brain regions than the hippocampus, preventing plasticity in these neurons. A recent report showed that PNNs are also distributed around excitatory pyramidal cells in the CA2 subarea of the mouse hippocampus and suppress excitability and plasticity of these neurons. However, the postnatal development of PNNs in the hippocampal CA2 subregion has not been well understood yet. In the present study, using immunohistochemical method, we focused on aggrecan, one of the chondroitin sulfate proteoglycans as a main component of PNNs, and found aggrecan expression in the pyramidal cell layer of the putative CA2 subregion at as early as postnatal-day 5 (P5), before the appearance of the CA2 subregion at P14, defined by regulator of G protein signaling 14 (RGS14), a CA2 marker protein. In the process of the investigation about the postnatal development, we also demonstrated that aggrecan immunoreactivity was stronger in the anterior sections of the CA2 subregion than the posterior sections and that the exclusive expression of aggrecan in the putative CA2 subarea started to appear in the most anterior section. These results

suggest that there might be some functional difference in the CA2 subarea along the anterior-posterior axis.

Disclosures: **A. Noguchi:** None. **N. Matsumoto:** None. **H. Tamura:** None. **Y. Ikegaya:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 650.03/B22

Topic: A.02. Postnatal Neurogenesis

Title: Newly generated cells in adult turtles are not GABAergic

Authors: *J. E. ALOUIDOR[1], A. S. POWERS[2]
[1]Neurosci., Stony Brook Univ., East Setauket, NY; [2]Psychology, Stony Brook Univ., Stony Brook, NY

Abstract: Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the adult vertebrate brain. As in many nonmammals, widespread adult neurogenesis occurs in the telencephalon of turtles. We studied whether the new cells are GABA-positive. Although they have been shown to be mainly neurons, nothing is known about the neurotransmitter used in the new cells in turtles. Furthermore, the neurotransmitter that regulates the different steps of adult neurogenesis specifically in turtles is unknown. While previous studies had demonstrated the presence of GABAergic cells in different regions of the turtle brain, this study aimed at determining whether GABAergic neurons are present in regions of neurogenesis in turtles, and whether GABA is present in the newly generated cells. Four adult painted turtles (*Chrysemys picta)* were kept under standard conditions and fed a standard diet. They were given 9 injections of BrdU (50 mg/kg) over a three-week period and euthanized 6 weeks after the first BrdU injection by an overdose of anesthetic and transcardial perfusion. The brains were cryoprotected and sectioned at 40 um. Some sections were stained with standard immunohistochemistry to determine the presence of GABAergic neurons. Other sections were stained with standard double immunofluorescence staining methods to determine whether the newly generated cells are GABAergic. As in previous studies, adult neurogenesis was seen near the lateral ventricles of the telencephalon in turtles. Moreover, our immunohistochemical technique revealed GABA-positive cells in similar regions near the lateral ventricles of the turtle telencephalon, with some revealing potential cell axons. Co-expression of GABA-positive cells with BrdU-positive cells was not observed, however, suggesting that none of the newly generated cells are GABAergic. GABAergic cells were found instead to be in close proximity to and sometimes even surrounding the newly formed cells. This finding shows continuity with mammals, where the new cells in the hippocampus are not GABAergic. A demonstration of continuity like this is consistent with the idea that GABA, as suggested in mammals, plays a key regulatory role in the formation and

synaptic integration of the newly synthesized cells; however, further studies are needed to support this hypothesis in turtles. Determining the neurotransmitter that regulates adult neurogenesis activities in turtles or the neurotransmitter used in the new cells could help to clarify why there is widespread neurogenesis in nonmammals compared to observed limited neurogenesis in mammals.

Disclosures: J.E. Alouidor: None. **A.S. Powers:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 650.04/B23

Topic: A.02. Postnatal Neurogenesis

Support: CRC 870 of the German Scienec Foundation

01 EO 0901 of the German BMBF

Title: Cell proliferation in the hindbrain of semi-intact *In vitro* preparations of Xenopus laevis tadpoles

Authors: V. SCHWARZ[1], R. SANCHEZ-GONZALEZ[2], J. NINKOVIC[2,3], *H. STRAKA[1]
[1]LMU Munich - Biocenter Martinsried, Planegg, Germany; [2]Inst. of Stem Cell Res., Helmholtz Ctr. Munich, Munich, Germany; [3]Biomed. Ctr., LMU Munich, Munich, Germany

Abstract: The considerable body growth during larval development in fish and amphibians is accompanied by an equally extensive increase in brain size and number of neuronal and non-neuronal elements. The continuous growth of the brain in anamniotes is to large extent achieved by an ongoing neurogenesis, as well as an increase in non-neuronal supporting cells and vascularization. Despite the vast amount of data on embryonic brain development, relatively little is known about cell proliferation at later ontogenetic stages. This prompted us to visualize cell proliferation in the hindbrain of *Xenopus laevis* tadpoles. Experiments were performed on semi-intact *in vitro* preparations at stage 50-52 and exploited a Bromodeoxyuridine (BrdU)-based identification of newborn cells and pursuit of the cells for up to 5 days after isolation of the preparation. BrdU-labeled cells were identified after tissue fixation, serial sectioning of the brain into 30 µm cross-sections and fluorescent antibody staining. This allowed determining site(s) and amount of cell proliferation, rate and extent of cell migration and fate over several days. Immunohistochemistry with antibodies against neuronal (HuC/D) and glial/progenitor markers (Sox10, Vimentin) was used to determine cellular profiles. Initial experiments indicated that incubation of tadpole preparations for 30 min in 5 mMol BrdU containing Ringer solution was optimal for a reliable labeling of proliferating cells. Following 30 min BrdU pulse labeling and

immediate fixation of the tissue, 30-50 newborn cells per section were predominantly encountered at the ventricular surface throughout the rostro-caudal extent of the hindbrain, although with rhombomere-specific regional differences in cell numbers. Following immediate fixation after BrdU pulse labeling, newborn cells were located within the epithelial layer but showed a ventro-lateral dispersion with increasing survival times up to 48 hours after pulse labeling. This migratory behavior, although limited in extent to ~50 µm, differed between cells and was generally larger for newborn cells medial to the sulcus limitans. Thus, rather than a homogeneous migratory wave, newborn neurons spread actively or were passively pushed from the proliferation zone at a differential rate. Immunohistochemistry of cellular profiles will determine cell fates, identify neuronal precursors and their insertion into defined circuitries with longer survival times. Moreover, the use of isolated *Xenopus* preparations for such an *in vitro* approach allows pharmacological manipulations of neurogenesis and subsequent migration, as well as the study of lesion-induced cell proliferation.

Disclosures: V. Schwarz: None. **R. Sanchez-Gonzalez:** None. **J. Ninkovic:** None. **H. Straka:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 650.05/B24

Topic: A.02. Postnatal Neurogenesis

Title: The effect of exercise on neurogenesis in the green anole lizard brain

Authors: C. A. FOLEY[1], J. J. RODDICK[1], E. C. MAGNUSON[2], A. Z. WANG[2], J. F. HUSAK[2], *R. E. COHEN[3]
[1]Minnesota State University, Mankato, Mankato, MN; [2]Univ. of St Thomas, St Paul, MN; [3]Biol. Sci., Minnesota State Univ. Mankato Dept. of Biol. Sci., Mankato, MN

Abstract: Previous studies in mammals have shown that exercise promotes neurogenesis in the hippocampus, but not much is known about how exercise impacts neurogenesis in reptiles. The hippocampus is responsible for behaviors such as spatial learning and memory, and is a major site of neurogenesis in the adult brain. The hippocampus also exhibits high levels of brain-derived neurotrophic factor (BDNF) and exercise has been associated with an upregulation of BDNF in the hippocampus. The green anole lizard (*Anolis carolinensis*) is an ideal model organism for studies of neuroplasticity due to dramatic seasonal changes in reproductive and aggressive behaviors, circulating steroid hormone levels and brain morphology. We examined how exercise impacts neurogenesis in the dorsal cortex (DC) and medial cortex (MC), the reptilian homolog of the hippocampus. To do that, two cohorts of adult breeding male lizards were injected subcutaneously with BrdU (50 mg/kg) once per day for five days prior to

treatment. The exercise group underwent forced exercise on a treadmill for 30 minutes/day for three weeks. The control group was handled and put back in the cage every day for three weeks. Two hours prior to sacrifice an additional bolus of BrdU was injected to mark newly proliferating cells. Tissue was collected, frozen and cryosectioned. An immunohistochemistry was performed for BrdU and Hu (neuronal marker), and double positive cells were counted in the DC and MC to examine the effects of exercise on new neuron integration. We also counted BrdU positive cells in the dorsal section of the subventricular zone to quantify neuronal progenitor cell proliferation between the two treatments. We will determine whether exercise impacts neurogenesis in the hippocampus and progenitor cell proliferation in the subventricular zone in reptiles, as it does in mammals. We also plan to utilize in situ hybridization to measure BDNF levels in the brain.

Disclosures: C.A. Foley: None. **J.J. Roddick:** None. **E.C. Magnuson:** None. **A.Z. Wang:** None. **J.F. Husak:** None. **R.E. Cohen:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 650.06/B25

Topic: A.02. Postnatal Neurogenesis

Support: Swedish Research Council

Title: Neural progenitor cells in cerebral cortex of epilepsy patients do not originate from astrocytes expressing GLAST

Authors: *M. PEKNA, M. CHEN, T. PUSCHMANN, U. WILHELMSSON, C. ÖRNDAL, K. MALMGREN, B. RYDENHAG, M. PEKNY
Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Adult neurogenesis in human brain is known to occur in the hippocampus, the subventricular zone, and the striatum. Neural progenitor cells (NPCs) were reported in the cortex of epilepsy patients, however their identity is not known. Since astrocytes were proposed as the source of neural progenitors in both healthy and diseased brain, we tested the hypothesis that NPCs in the epileptic cortex originate from reactive, alternatively, de-differentiated astrocytes that express glutamate aspartate transporter (GLAST). We assessed the capacity to form neurospheres and the differentiation potential of cells dissociated from fresh cortical tissue from patients who underwent surgical treatment for pharmacologically intractable epilepsy. Neurospheres were generated from 57% of cases (8/14). Upon differentiation, the neurosphere cells gave rise to neurons, oligodendrocytes and astrocytes. Sorting of dissociated cells showed that only cells negative for GLAST formed neurospheres. In conclusion, we show that cells with

neural stem cell properties are present in brain cortex of epilepsy patients, and that these cells are not GLAST-positive astrocytes.

Disclosures: **M. Pekna:** None. **M. Chen:** None. **T. Puschmann:** None. **U. Wilhelmsson:** None. **C. Örndal:** None. **K. Malmgren:** None. **B. Rydenhag:** None. **M. Pekny:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

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Program#/Poster#: 650.07/B26

Topic: A.02. Postnatal Neurogenesis

Support: NSERC Discovery Grant

NSERC PGSD

Killam Doctoral Scholarship

Title: Investigating homeostatic regulation of developmentally-born neurons following manipulations of adult neurogenesis in the dentate gyrus

Authors: ***S. P. CAHILL**[1], *S. P. CAHILL[1], A. MARTINOVIC[2], J. COLE[2], J. S. SNYDER[3]
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Abstract: Adult-born neurons contribute significantly to the synaptic circuitry in the dentate gyrus (DG) and play an important role in the cognitive and emotional functions of the hippocampus. An outstanding question is whether postnatal neurogenesis leads to continued growth in the DG or whether the addition of adult-born neurons is balanced by death of developmentally-born neurons. We have recently found that developmentally-born neurons die in early adulthood, unlike adult-born cells, which are known to remain stable (after reaching maturity). While adult-born neurons have enhanced plasticity and unique circuitry during their immature stages, many reports indicate that they may become functionally equivalent to neurons born in early postnatal development once they have reached maturity. These data collectively suggest that adult neurogenesis may serve to directly replace lost developmentally-born cells. Whether there is a causal, homeostatic relationship between numbers of developmentally-born and adult-born neurons remains unknown. We aimed to test this hypothesis by directly manipulating the adult-born neuronal population and examining how this impacts the number of surviving developmentally-born neurons in the DG. Male rats were injected with the mitotic marker BrdU at postnatal day 6, the peak of DG neuron birth, followed by either neurogenesis-promoting or suppressing treatments administered from 2 until 6 months of age. To suppress

adult neurogenesis we used transgenic GFAP-TK rats; at the end of treatment adult neurogenesis was reduced by 69%, as measured by doublecortin immunohistochemistry (IHC). To enhance adult neurogenesis, we subjected rats to alternating 4-week blocks of running and memantine, an NMDA antagonist, which we have found produces sustained increases in adult neurogenesis by 28% as measured by doublecortin IHC. According to a homeostatic relationship, we predict that supressing adult neurogenesis will increase survival of developmentally-born cells; conversely, we predict that increasing adult neurogenesis will reduce survival of developmentally-born cells. Finally, independent of changes in cell number, prolonged reductions or enhancements of adult neurogenesis may alter recruitment of DG neurons during learning experiences. To this end, all rats were exposed to a novel environment prior to the end of the experiment, to measure experience-driven expression of immediate-early genes in developmentally-born DG neurons. Collectively, these data will clarify whether there are interactions between neurons born at different stages of development, which may shape how information is retained in the hippocampus.

Disclosures: S.P. Cahill: None. **A. Martinovic:** None. **J. Cole:** None. **J.S. Snyder:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 650.08/B27

Topic: A.02. Postnatal Neurogenesis

Support: NIH grant P50 MH103222

State of Maryland grant 1TL4 MD009635

Title: Quantitative analysis of kynurenine II aminotransferase (KAT II/AADAT) gene in the rat brain reveals high expression in the Subventricular Zone, the rostral migratory stream and the corpus callosum

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Abstract: Kynurenic acid, a metabolite of the kynurenine pathway of tryptophan degradation, acts as an endogenous antagonist of alpha7 nicotinic and NMDA receptors and has been implicated in a number of neurophysiological and neuropathological processes including cognition and neurodegenerative events. Kynurenine aminotransferase II (KAT II/AADAT), the

enzyme that appears to be responsible for the formation of the majority of neuroactive kynurenic acid in the brain, has therefore raised significant interest. Using immunohistochemistry, this enzyme has been localized primarily in astrocytes throughout the adult rat brain (Guidetti et al., 2007), but further detailed neuroanatomical studies have not been conducted so far. In the present study, we employed quantitative *in situ* hybridization with radioactive riboprobes to analyze the relative expression of KAT II mRNA in the brain of adult, male rats, both in normal conditions and 6 hours after the administration of lipopolysaccharide (LPS; 2 mg/kg, ip). Specific hybridization signals for KAT II were detected, with the highest expression in the subventricular zone (SVZ), the rostral migratory stream and the floor of the third ventricle, followed by the corpus callosum and the stratum lacunosum moleculare (SLM) of the hippocampus. This pattern of mRNA expression was paralleled by differential protein expression, determined by serial dilutions of antibodies (up to 1:1 million) and was confirmed to be primarily astrocytic in nature. The mRNA signal in the SVZ and SLM was substantially increased by the LPS treatment without detectable changes elsewhere. These results demonstrate that KAT II is expressed in the rat brain in a region-specific manner and that gene expression in the SVZ and SLM is sensitive to inflammatory processes suggesting a so far unrecognized role for kynurenic acid in the brain's germinal zone.

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Poster

650. Postnatal Neurogenesis in an Array of Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 650.09/B28

Topic: A.02. Postnatal Neurogenesis

Title: Oligodendrocyte progenitor cells of the adult mouse suprachiasmatic nucleus may be a source of new neurons

Authors: D. H. BELIGALA, A. DE, H. J. MCQUILLEN, *M. E. GEUSZ
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Abstract: Studies have suggested that oligodendrocyte progenitor cells (OPCs) can give rise to new neurons in the hypothalamus of adult mice. Nascent neurons alter neuronal circuits and could provide flexibility in the timing of the circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus. Studies have not addressed whether ongoing or episodic OPC activity influences circadian clock functions. The aim of this study was to identify and confirm in vitro differentiation of OPCs from juvenile and adult mouse SCN. To limit the cultures to SCN cells, the optic chiasm and ependymal cell layer of the third ventricle were surgically removed from tissue explants trimmed from brain sections. Explants were placed in NeuralX medium

designed for OPC culture, which contained fibroblast growth factor-2, platelet-derived growth factor-AA (PDGF-AA), and GS22 supplement. By 4 days, explants attached to cell culture dishes and produced cells migrating from the edges and proliferating. Explants were removed after 11 to 25 days in culture. Immunocytochemistry and confocal microscopy was used to identify markers for OPCs (Olig2, PDGF receptor-α, and NG2), oligodendrocytes (myelin basic protein), neuroblasts (doublecortin), immature neurons (Class III-β tubulin), and mature neurons (NeuN). Cultures were enriched in cells expressing Olig2 (74.9%) and PDGFR-α (87.6%), along with fewer NG2-positive cells (7.19%). In a separate group, explant removal was followed by a medium exchange to BrainPhys supplemented with SM1 to determine whether the cultures can differentiate into neurons. After 4-5 days, the cell monolayer was rearranged into cell clusters, and the number of cells expressing neural markers increased: doublecortin (1.82-fold), class III-β tubulin (16.3-fold), NeuN (26.9-fold). After inducing differentiation, over 55% of the cells expressed Class III-β tubulin and 27% expressed NeuN. Myelin basic protein expression showed a 3.84-fold increase in the BrainPhys medium, suggesting a subset of OPCs differentiated into mature oligodendrocytes. These results indicate the potential for mature SCN tissue to form additional neurons, and it suggests a mode of possible plasticity within SCN neural circuits to provide adaptive or developmental changes in circadian rhythms.

Disclosures: D.H. Beligala: None. **A. De:** None. **H.J. McQuillen:** None. **M.E. Geusz:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

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Program#/Poster#: 650.10/B29

Topic: A.02. Postnatal Neurogenesis

Support: NIH/NINDS 4 R00 NS089938

Chronic Brain Injury Initiative seed grant

Title: CreER^{T2} mediated genetic recombination in adult murine neural stem and progenitor cells is induced by tamoxifen delivered via voluntary chow consumption

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Abstract: The tamoxifen (TAM)-sensitive Cre recombinase (CreER^{T2}) system has produced robust temporal control of genetic recombination in a variety of in vivo mouse models. Use of cell-specific expression of TAM-sensitive CreER^{T2} has become increasingly common in the field of adult neurogenesis as a technique for manipulating gene expression in neural stem and

progenitor cells (NSPCs) in adulthood. For example, the nestin promoter, which is selectively active in adult NSPCs, has been successfully used to drive CreER^{T2} expression and thereby genetic recombination of LoxP-flanked sites in NSPCs in the subgranular zone (SGZ) of adult NestinCreER^{T2} mice. Intraperitoneal injection of TAM in adult NestinCreER^{T2} mice is currently the standard method of TAM administration. Oral gavage has also been used previously. However, both TAM injections and oral gavage can be stressful for mice and are time and labor intensive for experimenters. Use of TAM mixed with chow has recently emerged as an efficient, low stress method for delivering TAM to tissues outside the brain. The efficacy of voluntary TAM consumption via chow for recombination in NSPCs has yet to be assessed. We therefore investigated the efficacy of TAM administered in a custom diet for inducing CreER^{T2} mediated recombination in NSPCs in the SGZ of adult mice. Nestin-CreER^{T2} mice were crossed with a commonly used Cre-sensitive reporter mouse, R26R-STOP-EYFP. Double mutant offspring (age 7-9 weeks) were provided a free feeding diet of Teklad Global 16% Protein Rodent Diet with 0.5g/kg of TAM. Following 1, 2, or 3 weeks of diet treatment, the mice were perfused and free floating immunohistochemistry was used to quantify efficiency and specificity of genetic recombination in NSPCs of the hippocampus. Our findings show that TAM chow effectively induces recombination in NSPCs, resulting in robust reporter expression. The highest rate of recombination was achieved with the 3 week treatment of TAM diet, whereas shorter treatments resulted in less recombination. Our findings demonstrate an alternative method for inducing TAM-mediated genetic recombination of LoxP-flanked sites in adult mouse NSPCs that reduces both stress for mice and experimenter labor compared to the field standard of intraperitoneal injections. Use of chow to deliver TAM could be particularly effective in models where animal stress or handling are of concern or where high rates of recombination following long-term TAM exposure are necessary.

Disclosures: B. Smith: None. **E.D. Kirby:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

Location: Halls A-C

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Program#/Poster#: 650.11/B30

Topic: A.02. Postnatal Neurogenesis

Support: Einhorn Family Charitable Trust

Title: Family Nurture Intervention in preterm infants increases early development of cortical activity and independence of regional eeg power trajectories

Authors: *M. MYERS, M. G. WELCH, P. G. GRIEVE, J. ISLER, R. STARK, J. BARONE
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Abstract: Aim: Premature delivery and maternal separation during long-term hospitalization increase infants' risk for neurodevelopmental disorders. A randomized controlled trial comparing standard NICU care with Family Nurture Intervention (FNI) demonstrated improvement across multiple mother and infant domains; these findings included increased EEG power in the frontal polar region at term age and greater independence of EEG power (decreased coherence) within and between frontal regions. Herein, we extend this analysis to include brain-wide cortical activity. **Methods:** EEG power data was assessed to quantify developmental trajectories of brain-wide cortical activity at all EEG frequencies and in both sleep states. **Results:** FNI significantly increased developmental rates of change in EEG power from 35 to 40 weeks at most frequencies over the entire cortex, with greater regional independence in those rates of change. **Conclusions:** The present study, taken with our prior EEG findings, strengthen the conclusion that facilitating co-regulation and emotional connection between mother and infant with FNI promotes cerebral cortical development of preterm infants. Importantly, this study's term frontal EEG power and brain-wide developmental change findings indicate that term-age EEG and preterm EEG may provide biomarkers for developmental risk in preterm infants as well as a proximal marker of efficacy of early intervention.

Disclosures: M. Myers: None. **M.G. Welch:** None. **P.G. Grieve:** None. **J. Isler:** None. **R. Stark:** None. **J. Barone:** None.

Poster

650. Postnatal Neurogenesis in an Array of Models

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Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant NS064135

NIH Grant NS064135S1

Title: Experience-dependent regulation of Cajal-Retzius cell networks in the developing and adult mouse hippocampus

Authors: *G. MACCAFERRI[1], S. K. LEE[1], T. I. NEBLETT[1], G. M. RUNE[2], M. ANSTÖTZ[1,2]
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Abstract: In contrast to their near-disappearance in the adult neocortex, Cajal-Retzius cells have been suggested to persist longer in the hippocampus. A distinctive feature of the mature hippocampus, not maintained by other cortical areas, is its ability to sustain adult neurogenesis. Here, we have investigated whether environmental manipulations affecting hippocampal

postnatal neurogenesis have a parallel impact on Cajal-Retzius cells. We used multiple mouse reporter lines to unequivocally identify Cajal-Retzius cells and quantify their densities during postnatal development. We found that exposure to an enriched environment increased the persistence of Cajal-Retzius cells in the hippocampus, but not in adjacent cortical regions. We did not observe a similar effect for parvalbumin-expressing interneurons, which suggested the occurrence of a cell type-specific process. In addition, we did not detect obvious changes either in Cajal-Retzius cell electrophysiological or morphological features, when compared to what previously reported in animals not exposed to enriched conditions. However, optogenetically-triggered synaptic output of Cajal-Retzius cells onto local interneurons was enhanced, consistent with our observation of higher Cajal-Retzius cell densities. In conclusion, our data reveal a novel form of hippocampal, cell type-specific, experience-dependent network plasticity. We propose that this phenomenon is required for the correct regulation of enrichment-dependent enhanced hippocampal postnatal neurogenesis.

Disclosures: G. Maccaferri: None. **S.K. Lee:** None. **T.I. Neblett:** None. **G.M. Rune:** None. **M. Anstötz:** None.

Poster

651. Modeling Neurodevelopmental Disease

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Program#/Poster#: 651.01/B32

Topic: A.07. Developmental Disorders

Support: NIH/NIMH Grant R01MH105610

The Nancy Lurie Marks Family Foundation

Title: Enhancing plasticity rescues social behavioral deficits in Pten haploinsufficient mice

Authors: *A. E. CLIPPERTON-ALLEN, A. ZHANG, O. S. COHEN, D. T. PAGE
Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: *Pten* germline haploinsufficient (*Pten*$^{+/-}$) mice, which model macrocephaly/autism syndrome, show deficits in social behaviors, as well as early brain overgrowth and cortical-subcortical hyperconnectivity. Previous work in this model has indicated that altered neuronal connectivity may be a substrate for social behavioral deficits. We hypothesized that exposing *Pten*$^{+/-}$ mice to environmental enrichment after brain overgrowth has occurred may facilitate adaptation to abnormal “hard-wired” connectivity through enhancing synaptic plasticity. To test this hypothesis, wild type and *Pten*$^{+/-}$ mice were reared from weaning under either standard (4-5 mice per standard-sized cage, containing only bedding and nestlet) or enriched (9-10 mice per large-sized cage, containing objects for exploration and a running wheel, plus bedding and

nestlet) conditions for 35 days. Adult mice were then tested using several social and non-social assays in which *Pten*$^{+/-}$ mice display deficits. Environmental enrichment rescued sex-specific deficits in social approach behavior in *Pten*$^{+/-}$ mice, but did not rescue other non-social deficits in these animals. Ongoing experiments are examining the effects of environmental enrichment on network activity in brain areas important for processing social information and on the expression of genes related to synaptic plasticity. Together, our results indicate that environmental enrichment can rescue social behavioral deficits in *Pten*$^{+/-}$ mice, possibly through a synaptic plasticity mechanism.

Disclosures: A.E. Clipperton-Allen: None. **A. Zhang:** None. **O.S. Cohen:** None. **D.T. Page:** None.

Poster

651. Modeling Neurodevelopmental Disease

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Topic: A.07. Developmental Disorders

Support: NIMH Grant MH101584

Seaver Foundation

HFSP RGP0019/2015

Title: Study of the oxytocin system in two rat models for autism

Authors: *H. HARONY-NICOLAS[1], M. ELIAVA[2], L. KORO[3], M. RIAD[3], C. GOLDEN[4], S. WAGNER[5], V. GRINEVICH[6], J. D. BUXBAUM[7]
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Abstract: Abstract:
Social behavior deficits are a core symptom in autism spectrum disorder (ASD), which up to date have no pharmacological treatment. The hypothalamic oxytocin (OXT) system is a well-known modulator of social behavior, which brought interest in using the OXT peptide to treat social behavioral deficits. Our studies in a rat model for ASD, the *Shank3*-deficient rat, demonstrated that intracerebroventricular OXT administration ameliorates synaptic plasticity, attentional and social memory deficits. Clinical trials of OXT in ASD produced equivocal results raising

questions about (1) whether this equivocally is driven by the heterogeneity in ASD, where some ASD subgroups may benefit better than others and (2) if the efficacy of OT treatment is dependent on the functionality of the OXT system and/or is sensitive to specific developmental window. Addressing these questions is challenging due to the lack of predictive biomarkers and the lack of sufficient and diverse postmortem samples to determine how OXT-system is affected in different ASD subjects. Genetic animal models with mutations in ASD-associated genes are powerful tool to help overcome these limitations, yet to date only few studies have employed these models to tackle the limitations in clinical studies. Our study is focused on examining the effect of ASD-associated mutations on the integrity and functionality of the OXT hypothalamic system and on assessing the effect of OXT treatment on behavioral deficits during different developmental stage. For this purpose, we are using two rat models with mutations in ASD-associated genes with relatively common and high penetrant in ASD and intellectual disability: (1) the *Shank3*-deficient rat model with a mutation in the *Shank3* gene, which is implicated in Phelan McDermid syndrome (PMS) and (2) the *Fmr1*-rat model with a mutation in the *Fmr1* gene, which is implicated in Fragile X syndrome (FXS). Our characterization of the OXT neurons in the hypothalamic periventricular nucleus (PVN) of *Shank3*-knockout rats revealed increased OT immunoreactivity and dendritic swelling, suggesting that OXT release is impaired. In *Fmr1*-rats, we found decreased numbers of OXT neurons in the PVN. Our findings suggest that the OXT system may be impaired in subset of individuals with ASD (i.e., with PMS and FXS) and imply that treatment with OXT may be beneficial in these individuals, where the integrity of the OXT system could be potentially disturbed.

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Poster

651. Modeling Neurodevelopmental Disease

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Topic: A.07. Developmental Disorders

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Beatrice and Samuel A. Seaver Foundation (DP, NJF)

Title: Uncovering the role of long non-coding RNAs (lncRNAs) in autism spectrum disorders using integrated transcriptomic approaches

Authors: N. J. FRANCOEUR[1], M. J. GANDAL[3], K. A. SARPONG[1], J. S. JOHNSON[1], P. SKLAR[1], H. VAN BAKEL[2], D. H. GESCHWIND[3], *D. PINTO[1]

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Abstract: The contribution of non-coding genomic elements remains largely unexplored in autism spectrum disorders (ASD). LncRNAs are increasingly recognized for their role in transcription regulation, and likely contribute to transcriptome dysregulation in ASD.
We are applying a combination of short-read and long-read RNA-Seq, with and without lncRNA capture to unveil the role of lncRNAs in ASD. As lncRNAs are poorly represented in standard RNA-Seq experiments, we used capture RNA-Seq (Capture-Seq) to quantify lncRNA expression in postmortem prefrontal cortex and cerebellum tissue in a cohort of 40 ASD and control samples. We additionally combined full-length isoform sequencing (Iso-Seq) with capture (Capture-IsoSeq) to build a comprehensive map of brain-expressed lncRNAs.
The enrichment by Capture-Seq increased the lncRNA fraction of our RNA-Seq datasets from 5% to 57%. We identified 28 differentially expressed (DE; FDR<0.05) lncRNAs and transcripts of unknown coding potential (TUCPs) in ASD samples compared to controls. A “guilt-by-association” analysis further revealed genes under putative cis-regulation of DE-lncRNAs that are implicated in pathways dysregulated in ASD. Finally, Capture-IsoSeq profiling identified ~3,600 novel multiexonic lncRNA/TUCP isoforms expressed in prefrontal cortex. We have identified many DE lncRNA/TUCP transcripts in a cohort of 40 ASD and control samples from two different brain regions as a first step towards understanding the role of lncRNAs in ASD etiology.
In summary, capture enriched sequencing substantially improves our ability to profile lncRNA expression and reconstruct poorly annotated lncRNA isoforms.

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Poster

651. Modeling Neurodevelopmental Disease

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Topic: A.07. Developmental Disorders

Support: NIH/NINDS R01NS076708

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NIH/NIMH R01MH096816

Title: mTORC2 dysfunction underlies the neuronal physiological and behavioral abnormalities in Pten-deficient mouse model of autism

Authors: *C.-J. CHEN[1], M. SGRITTA[1], R. D. LUCERO[2], J. L. NOEBELS[2], M. COSTA-MATTIOLI[1]
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Abstract: Autism Spectrum Disorder (ASD) is one of the most common neurological disorders characterized by abnormal social behavior, deficits in communication, restricted/repetitive stereotype behaviors and, often, intellectual disability. In addition, epilepsy is also common in ASD patients. The mechanistic target of rapamycin (mTOR) acts as a highly conserved signaling hub that integrates neuronal activity and a variety of synaptic inputs. Loss-of function mutations in phosphatase and tensin homolog (PTEN), a negative regulator of mTOR signaling, were associated with syndromic ASD. While PTEN-deficiency leads to the hyperactivation of both mTOR complexes (mTORC1 and mTORC2), it is generally believed that dysregulation of mTORC1-mediated protein synthesis leads to ASD phenotypes. However, most of the evidences supporting a role for mTORC1 in ASD-like phenotypes relied on the chronic pharmacological inhibition of mTOR by rapamycin, which blocks the activity of both mTORC1 and mTORC2 in brain. To investigate the selective involvement of mTOR complexes in PTEN-associated ASD, we generated mice lacking PTEN, PTEN and Raptor (defining component of mTORC1), or PTEN and Rictor (defining component OF mTORC2) in the forebrain. Mice lacking Pten in the forebrain showed up-regulation of both mTORC1 and mTORC2 activities, exhibited ASD-like behavior, seizures, hyper-excitability in hippocampal neurons, and they died between 7-8 weeks of age. Surprisingly, genetic inhibition of mTORC1 had no effect on PTEN induced pathology. By contrast, genetic inhibition of mTORC2 in PTEN-deficient mice prolonged their lifespan, ameliorated seizure activity, normalized neuronal excitability, and restored cognitive and social behaviors. The changes in neuronal function in Pten-Rictor deficient mice were accompanied by restoration of Akt-mediated glucose metabolism, which was disrupted in the Pten-deficient brain. Our study not only provides advances in the understanding of the role of different mTOR complexes in ASD, but also suggests potential new mTORC2-based treatment for ASD and related neurodevelopmental disorder.

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Poster

651. Modeling Neurodevelopmental Disease

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Topic: A.07. Developmental Disorders

Title: Loss of the sulfate transporter Slc13a4 impairs social interactions and adult neurogenesis in mice

Authors: *Z. ZHANG[1,2], M. PIPER[1], P. DAWSON[2], D. SIMMONS[1,2]
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Abstract: SLC13A4 is a sodium-dependent sulfate transporter which is primarily expressed in the placenta and brain. During our earlier investigations of placental *Slc13a4* function, we observed that *Slc13a4* haploinsufficiency caused abnormal maternal behaviours, resulting in a postpartum loss of pups. In the current study, we investigated potential reasons underlying this phenomenon. We, and others, found *Slc13a4* gene expression to be predominately restricted to the choroid plexus (ChPs) and pia mater of the brain, suggesting a role in regulating sulfate levels in the brain. We then localized SLC13A4 protein to the basolateral membrane of ChP epithelium, consistent with a role in sulfate uptake from the blood. Tail vein injections of ^{35}S-labelled sulfate corroborate this hypothesis, as *Slc13a4*$^{+/-}$ mice uptake ~50% less $^{35}SO_4^{2-}$ into the brain than wildtype controls. Abnormal maternal behaviours usually occur along with other impaired behaviours. Initial behavioural, motor and metabolic tests did not reveal differences between*Slc13a4*$^{+/+}$ and *Slc13a4*$^{+/-}$ animals, including olfactory discrimination, forced swim test, hanging wire test, food and water intake, and body weight and fat composition. However, we did observe profound defects in social interaction (separate reunion test and intruder test) and social memory, commonly seen in animal models of autism spectrum disorders (ASDs). Some of ASDs mouse models and human autism patients also display alterations in neurogenesis; we performed BrdU injections in 10-12-week old adult mice and observed an increase in neural stem cell proliferation within the subventricle zone (SVZ). We then deleted *Slc13a4* only in adult mice (~10 weeks of age), by crossing *Slc13a4*$^{flx/flx}$ with the UBC-Cre-ER^{T2} deleter line, and found that none of these phenotypes developed, suggesting a developmental origin to the phenotypes we observed previously. Indeed, when we deleted *Slc13a4* at postnatal day 7, *Slc13a4*$^{+/-}$ mice developed all the deficits in social interaction and altered neurogenesis at 12 weeks of age. Therefore, SLC13A4 activity appears to be essential during an earlier developmental window in order to prevent the onset of social interaction and neurogenesis impairments in later adult life. In summary, our current findings regarding SLC13A4 function highlights the critical role of *Slc13a4* activity in regulating animal behaviour and promoting a proper microenvironment which is essential for homeostasis of adult neurogenesis during postnatal development. Disruption of *Slc13a4* during this critical window appears to promote the development of autism-like phenotypes in adults.

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Poster

651. Modeling Neurodevelopmental Disease

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Topic: A.07. Developmental Disorders

Support: NIH R01 CA74177

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DoD NF150083

Title: The role of Ras pathway in social and communication behaviors in Nf1 mice

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Abstract: Neurofibromatosis type 1 (NF1) is a common human genetic disorder caused by a loss-of-function mutation in one copy of the NF1 gene (*NF1*$^{+/-}$). A majority of children with NF1 suffer from some learning or cognitive difficulties with a third associated with autism spectrum disorders (ASD). Recent studies have also reported that a significant number of children with NF1 demonstrate disruptions in communication that are independent of their attention and learning problems. The NF1 gene encodes neurofibromin, a p21 Ras GTPase-activation protein (GAP), and its activity is mediated by its GAP domain. Isoform 1 of the NF1 gene expresses the full length NF1 transcript. One particular splice variant, exon 23a, adds 21 amino acids in the NF1 GAP region and weakens its ability to control Ras signaling. We have previously demonstrated that deletion of a single *Nf1* allele (*Nf1*$^{+/-}$) in male mice leads to hyperactivation of Ras pathway associated with deficits in social memory. However, little is known about the role of Ras hyperactivation within key neural networks in regulating communication and stereotypical behaviors. To further characterize the behavioral phenotype of *Nf1*$^{+/-}$ male mice and to determine the role of of Ras hyperactivation in ASD phenotypes, we compared wildtype (WT), *Nf1*$^{+/-}$, *23a*$^{+/+}$, and *23a*$^{+/+}$/*Nf1*$^{+/-}$ mouse strains that were bred from a C57BL/6J background to examine differences in female-induced ultrasonic vocalizations (USVs), social preference behavior in a three-chambered apparatus, and stereotypic rearing. We also mapped

the neural networks involved in these behaviors by examining the differential activation pattern of pERK immunoreactivity within neuronal cells in WT compared to *Nf1*$^{+/-}$, *23a*$^{+/+}$, and *23a*$^{+/+}$/ *Nf1*$^{+/-}$ mice. Female-induced USVs were disrupted in *Nf1*$^{+/-}$, *23a*$^{+/+}$, and *23a*$^{+/+}$/ *Nf1*$^{+/-}$ compared to WT mice. Insertion of exon 23a did not affect social preference compared to WT, however *23a*$^{+/+}$/ *Nf1*$^{+/-}$ mice exhibited significant short- and long-term social deficits. Furthermore, *Nf1*$^{+/-}$ mice demonstrated increased duration and frequency of rearing in a novel test cage compared to WT animals. Similar to the Ras increases observed in the BLA, increased pERK immunoreactivity was noted in the prefrontal cortex of *Nf1*$^{+/-}$ mice compared to WT. Our results suggest the importance of the Ras pathway in social but not in communication behaviors. Our data also provide additional information about the neural circuits and mechanisms relevant to other forms of Ras-and synaptopathy-induced ASD syndromes and important leads to developing deficit-specific therapies for NF1 children.

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Poster

651. Modeling Neurodevelopmental Disease

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Topic: A.07. Developmental Disorders

Support: Partnership for Pediatrics Epilepsy Research Grant

Title: Deletion of semaphorin 3F in interneurons is associated with decreased GABAergic neurons, autism-like behavior, and increased inflammation and oxidative stress

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Abstract: The neuropathology of all neural circuits in ASD are dependent on changes in functional connectivity via the excitation/inhibition (E/I) ratio, that impact routine neurotransmission, synaptic plasticity, and network function. We were the first to publish an extensive investigation of an animal model of autism and epilepsy (Barnes et al., 2009). The semaphorin/neuropilin gene family, an ASD associated set of genes, are guidance cues that control processes and cell motility in a wide variety of tissues. In the developing brain, these cues control interneuron migration/cell numbers, regulate neurite outgrowth (axon/dendrite), and control both GABA/excitatory synaptogenesis. Several groups, including our own, have noted

behavioral phenotypes consistent with autism in both the semaphorin 3F (Sema 3F) and neuropilin 2 (NRP2) knockout mice. Similar to NRP2 KO mice, the interneuron specific but not excitatory neuron specific knockout of Sema 3F had decreased Parv+ and NPY+ interneurons and increased epileptogenesis with decreased social behaviors and increased repetitive behaviors compared to wild type littermates. We aimed to determine whether semaphorin 3F KO mice also presented with brain inflammation and oxidative stress that could be associated with ASD-like behavior. The significant increase in immunoreactivity of Iba1, a microglial marker, and of oxidative stress markers (DHE, 4HNE, iNOS, and 3-nitrotyrosine) suggest increased inflammation and oxidation products both within the glia and neurons of the interneuron specific Sema 3F KO mouse. Thus, although this is a single ASD associated gene KO mouse, these data strongly suggest that genetic mouse models of autism with markers of inflammation will be an excellent tool to investigate the role of genomics, environmental factors influencing the immune system (metals, obesity), clinical endophenotypes, and metabolic conditions. Most importantly, these models and others can define molecular mechanisms influencing the interactions among organ systems contributing to ASD brain dysfunction.

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Poster

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Support: Healthcare Technology R&D project (No: HI12C0021) by Ministry of Health and Welfare, Republic of Korea

Title: Novel de novo genetic variants in autism spectrum disorder in Korean population

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Abstract: Objectives: The objective of this study is to examine *de novo* genetic variants of autism spectrum disorder (ASD) and to explore their characteristics using network analyses. **Methods:** The probands with ASD and their biological parents were recruited. We ascertained diagnosis based on DSM-IV-TM criteria, using Autism Diagnostic Observation Schedule and

Autism Diagnostic Interview - Revised. We selected probands with typical phenotypes in all domains and with nonverbal or phrase speech level of language. In the pilot phase, we performed whole exome sequencing (WES) with minimum 50x for 13 families. In the extended phase, additional WES was performed for 38 families, at least 100x depth and high-coverage pooled sequencing for their parents (250 million paired-end reads for mothers and 236 million for fathers). All the sequence reads were mapped onto the human reference genome (hg19 without Y chromosome). We used BWA, Picard, GATK (McKenna, Aaron, et al., 2010) and in-house custom annotation pipeline for variants discovery. We selected *de novo* mutation candidates from each proband which are not detected in two pooled samples and pathogenic variants. For validation, Sanger sequencing was applied on ABI 3730 or Sequenom MassARRAY system (Sequenom, Inc., San Diego, CA). Network analyses was performed using pathway studio (RELX, 2016) and ingenuity pathway analysis (Quiagen, 2017). Connectivity map was generated with reference to previously known candidate genetic variants of ASD.
Results: Fifty one subjects with ASD (4 females, 77.56±31.22 months, IQ 60.04±14.79) and their families were included. Forty four *de novo* variants from 46 families are validated. Clinical variables did not show significant differences between subjects with and without *de novo* variants. KCTD9, HAX1, IWS1, NFKB1, RUFY1, ATXN1, SCAL25A13, PFKP RNH1, RASAL1, SNF8, ELL, PPP1R16B genes were revealed to interact with previously known ASD risk genes. In the network analyses, *de novo* variants are involved in the gene networks related to hereditary disorder, developmental and neurological disorder, neuronal injury and abnormalities, and nervous system development and function.
Conclusions: In the WES of family samples of ASD, we observed novel *de novo* variants which are assumed to contribute to development of ASD with relatively low functioning.

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Poster

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Support: T32GM007347

P50MH096972

Title: ASD-associated behavioral traits and dopaminergic abnormalities in the SERT G56A mouse

Authors: *G. E. DICARLO[1], K. E. BUNDSCHUH[1], M. T. WALLACE[2]
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and interaction and by patterns of restricted interests and repetitive behaviors. Moreover, nearly 90% of individuals with ASD experience some alteration in sensory function. One key brain region for the integration of information related to social communication, and for the elaboration of sensorimotor behaviors, is the striatum. The striatum is highly enriched in both dopaminergic and serotonergic projections, and recent work has suggested an altered developmental trajectory of the striatum in individuals with ASD. While both serotonergic and dopaminergic dysfunction have been implicated in ASD and these two neurotransmitter systems are known to interact at the cellular level, little work has focused on understanding how dysfunction in one of these neurotransmitter systems cascades into dysfunction of the other. In this study, we used a mouse expressing an ASD-associated point mutation in the serotonin transporter (SERT) to determine the impact of this mutation on striatal dopaminergic function. This mutation, a glycine to alanine substitution at site 56 (SERT G56A), is known to increase the firing rate of serotonergic neurons, to increase the sensitivity of type 1A and 2A serotonin receptors, and to enhance the rate of serotonin clearance from the extracellular space. In addition to previous work showing altered social communication and repetitive behaviors in these animals, our current work demonstrates early-life deficits in social preference and communication as well as altered maternal care towards animals homozygous for this mutation. To probe the effect of this mutation on the dopaminergic system, we measured expression levels of the dopamine transporter (DAT) and the concentration of dopamine in the striatum of mice homozygous for the SERT G56A mutation. We found that SERT G56A homozygous animals exhibit a significant reduction in expression of the dopamine transporter (DAT) in the striatum when compared to wild-type littermates, without change in the concentration of dopamine or its metabolites in the striatum. To explore anatomical correlates of these findings, we performed *ex vivo* diffusion kurtosis imaging studies, which suggested microstructural abnormality in the striatum of the SERT G56A mice. This works provides evidence for striatal dopaminergic dysfunction as the result of an ASD-associated mutation in the serotonin system and supports future research directed toward uncovering the role of dopaminergic dysfunction in ASD.

Disclosures: G.E. Dicarlo: None. **K.E. Bundschuh:** None. **M.T. Wallace:** None.

Poster

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CIHR postdoctoral fellowship

Title: Resting-state functional connectivity in homozygous Cntnap2 knockout mice

Authors: *K. Y. CHOE[1], M. SAFRIN[2], N. G. HARRIS[3], D. H. GESCHWIND[2]
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Abstract: Neuroimaging studies in individuals diagnosed with autism spectrum disorders (ASD) have repeatedly reported aberrant neural connectivity, including decreased long-range and increased short-range functional connectivity. Understanding the mechanistic basis for these changes warrants the use of animal models with strong construct and face validity. Mice lacking Contactin-Associated Protein-Like 2 (Cntnap2), a highly penetrant major gene form of ASD, display the core behavioral phenotypes of ASD (Penagarikano et al., 2011). A recent report has demonstrated reduced local and long-range prefrontal functional connectivity in these mice (Liska et al., 2017). To assess disruptions at a whole brain network level, we performed high field (7 Tesla) resting-state functional magnetic resonance imaging, 2000/19ms repetition and echo time for 5 mins, in dexmedetomidine-sedated wild-type (WT, n=20) and Cntnap2 knockout (KO, n=24) male and female mice. Global network connectivity measures were calculated over a 5-50% network density range, using the network-based statistic approach (Zalesky et al., 2010). Compared to WT controls, we observed subtle trends toward reductions (~10-15%) in global efficiency, mean local efficiency, and mean clustering coefficient in KO mice. These results suggest both global and local decreases in functional connectivity. No genotype differences were found in characteristic path length and modularity. To determine the brain regions that may underlie this altered global connectivity, we analyzed functional connectivity at the regional level, defined by a modified, 3D Allen mouse brain parcellated atlas (23 bilateral regions, 64 in total). At 35% network density, we found significantly lowered ($p<0.05$) functional connectivity in KO mice in association areas, piriform cortex and dorsal peduncular areas (vs. WT: -22.4±7.2%, -26.8±7.0%, -18.4±5.0%, respectively). These results, while preliminary, are consistent with previous observations, and highlight potential parallels between functional connectivity alterations in Cntnap2 KO mice and in individuals with ASD. We are now extending these pilot data to validate the generalizability and reproducibility of these results.

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Poster

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Topic: A.07. Developmental Disorders

Support: Program of International S and T Cooperation(2015DFA31580)

Title: Dip2a mutant mice and gene expression pattern

Authors: *J. MA[1], L. ZHANG[2], Y. WANG[1], C. SU[1], Y. ZHENG[2], X. ZHU[1]
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Abstract: Disconnected (disco)-interacting protein 2 homolog A (DIP2A) is a member of the DIP2 protein, which is evolutionarily conserved in organisms from *C. elegans* to humans. DIP2A is firstly identified and characterized in *Drosophila* and interacted with the transcription factor *disco*. Recently, studies on autism spectrum disorder (ASD) patient using copy-number variants (CNV) analysis have pointed out that *Dip2a* is a risk factor for ASD occurrence. Patients with a ~3-Mb terminal deletion of chromosome 21p22.3, including *Dip2a*, showed substantial susceptibility to ASD. These data provided strong evidence for *Dip2a* mutations in various cognitive and social defects. However, roles of DIP2A in mammalian are still obscure. Thus clarifying the functions of DIP2A in neurodevelopment could provide new insights for ASD nosogenesis. To investigate DIP2A function and expression in mouse brain, two mouse models were generated using CRISPR/Cas9 technology, including an entire *Dip2a* gene deletion mutant model (about 65kb) and a β-galactosidase (lacZ) reporter gene knock-in mouse model. Our preliminary results showed the mutant mice were fertile with no obvious phenotypic difference, including life span and body weight. More characterization work is underway to study the impact of *Dip2a* deletion on neuronal development. Using lacZ staining analysis we found DIP2A is broadly expressed in neuronal, reproductive and vascular tissues, as well as in heart, kidney, liver and lung, which are all derived from ectoderm in mouse embryo. A further investigation in brain tissue showed DIP2A is highly expressed in cortex, hippocampus and thalamus, including amygdala, which are the regions rich of projection neuron soma. In comparison, its expression in the striatum was low, where are mostly nerve fibers. Then, we co-immunostained lacZ with a variety of cell type-specific markers in *Dip2a*$^{lacZ/+}$ mice to investigate its expression in different neuron developmental stages. DIP2A was only detected in in part of immature neurons and all mature neurons, but not in the neuroblasts, type 1 or type 2 radial glia-like cells as well as astrocytes. Collectively, these data suggest that DIP2A is likely to function in projection neuron maturation.

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Poster

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Topic: A.07. Developmental Disorders

Title: A mouse model of the human 15q13.3 microdeletion syndrome (Df(h15q13)/+) with reduced alpha7 nAChR expression exhibits no deficits in hippocampal excitatory transmission and activity-regulated gene expression

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Abstract: The 15q13.3 microdeletion syndrome is associated with high risk for epilepsy, intellectual disability, schizophrenia, autism spectrum disorder (ASD), and ADHD. However, there is incomplete penetrance, and the phenotype is heterogeneous. Most human carriers have a heterozygous deletion which encompasses seven genes: CHRNA7, FAN1, MTMR10, OTUDA7A, TRPM1, and KLF13. The alpha7 nicotinic acetylcholine receptor (α7 nAChR) subunit, encoded by CHRNA7, is involved in excitatory synapse formation, and haploinsufficiency of the CHRNA7 is believed to be causative for most of the behavioral phenotypes in human carriers. A translationally relevant mouse model with a homologous deletion on the mouse chromosome 7qC, Df(h15q13)/+ was recently created (Fejgin et al. 2014), which displays behavioral features of the 15q13.3 syndrome. In this study, we used wild-type (WT) and heterozygous (HT) male and female Df(h15q13)/+ mice to test the hypothesis that HT mice have reduced excitatory transmission in the hippocampus, and altered basal expression of activity-regulated genes. Using receptor autoradiography, we first quantified the numbers of α7 nAChR binding sites in cortex and hippocampus, which were decreased by ~50% in the HT compared to the WT mice (n=8, $p<0.001$). To determine differences in the neurophysiology, young adult male and female WT and HT mice were used for recordings of field excitatory postsynaptic potentials (fEPSPs). Hippocampi were removed, and transverse 450 µm slices were cut from the middle third of each hippocampi. EPSPs were evoked via a bipolar stimulating electrode placed in Schaeffer collaterals with dendritic fEPSPs recorded in the stratum radiatum. Input/output (I/O) curves were generated by increasing stimulation intensities, and the slope of the dendritic response was measured. Analysis revealed that there was no significant difference between genotype in either male or female mice in the slope of the I/O curves (n=4-7), and no difference was detected in long-term potentiation (LTP) after theta-burst stimulation (n=3-6). Thus, no significant difference in excitatory transmission was found in the hippocampus between WT and HT mice. Furthermore, there was no significant difference between WT and HT mice (n=4) in basal mRNA expression of the activity-regulated genes Arc, BDNF, c-Fos, Egr-1 and Npas4, as determined by in situ hybridization. In summary, despite significantly decreased expression of α7 nAChR binding sites, there was no apparent alteration in hippocampal neurophysiology in terms of fEPSPs or LTP, or in expression of activity-regulated genes in mice with a heterozygous deletion.

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Poster

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Title: MTOR signaling modulates migration of cortical interneurons in the LgDel model of 22q11.2 DS

Authors: *E. M. PARONETT[1], D. W. MEECHAN[2], C. A. BRYAN[2], E. A. RADIN[2], A.-S. LAMANTIA[2], T. M. MAYNARD[2]
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Abstract: Disruptions in interneuron connectivity have been identified as a key pathological target in several behavioral disorders, including autism and schizophrenia. We have previously shown in a mouse model of 22q11.2 Deletion Syndrome (22q11.2 DS), a neurodevelopmental syndrome strongly associated with autism and schizophrenia, that the migration of interneurons into the cortex is delayed and disrupted, leading to an aberrant distribution of interneurons in the cortex. This disruption in interneuron migration is due to dysregulated signaling via the Cxcr4 cytokine receptor, which has been shown to act via modulation of the mammalian target of rapamycin (MTOR) signaling pathway in several models of cell motility. We have used a conditional genetic approach to disrupt MTOR signaling in both LgDel and WT mice, by using a Dlx5/6-Cre line to specifically ablate either the MTOR-repressor Tsc2, or Mtor itself, in interneuron precursors. We found that heterozygous loss of Mtor amplifies the migration defects normally observed in the LgDel cortex, with compound LgDel;$Mtor^{+/-}$interneurons showing disorganized distributions. In contrast, when the LgDel mutant is complemented with an mTOR "gain of function" mutation (LgDel;$Tsc2^{+/-}$), few interneurons enter the cortex at E14. Additionally, signaling intermediates downstream of MTOR appear to have altered expression in the LgDel cortex. Thus, MTOR signaling appears to be disrupted in the cortex of the LgDel mouse model, leading to altered neuronal circuitry. MTOR signaling is itself implicated in behavioral disorders such as autism, and multiple genetic syndromes with autism-like behavioral consequences have been described that involve Mtor and its interacting partners. Therefore, it is possible that this signaling mechanism may be a point of convergence between 22q11.2 DS and other, genetically distinct forms of syndromic behavioral disorders.

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Poster

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Title: Deficient of autism susceptibility gene Protocadherin 9 leads to abnormalities in vestibular response and emotional behavior in mice

Authors: *S. HIRANO[1], T. FURUSE[2], S. WAKANA[2], S. NAGAO[3], M. KUDOH[3], Y. SATO[1], K. OKANO-IMAI[1], K. YOSHIZAWA[4]
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Abstract: Protocadherins constitute the largest family of cadherin superfamily genes. Protocadherin 9 (Pcdh9) is reported to be an autism susceptibility gene (Marshall et al. 2008). In mouse, Pcdh9 is expressed in various parts of the developing nervous system including the oculomotor and vestibular systems (Asahina et al. 2012). To determine the roles of Pcdh9 in the nervous system, we generated a Pcdh9 knock-out (Pcdh9-KO) mouse line (established by RIKEN CLST LARGE), and analyzed its histology, vestibular function, and behavior.
No significant morphological abnormalities were detected in any tissues including the liver, stomach, intestine, heart, kidney, lung, etc. in Pdh9-KO mice through analysis of general histology with HE staining, although their body weight was low. The gross morphology of the

brain and major neural tracts of Pdh9-KO mice visualized with the anti-neurofilament antibody was normal.
Then, we examined roles of Pdh9 in neural functions. We tested the vestibular response of Pcdh9-KO mice, as reported in the previous study of Shutoh et al. (2006). Gains of the horizontal optokinetic response, but not those of the horizontal vestibular-ocular reflex, were significantly reduced compared with those of wild-type mice. Second, we tested the behavior of Pcdh9-KO mice systematically using protocols of the Japan mouse clinic (RIKEN BRC), which includes light/dark transition test, open-field, Crawley's three chamber test, Home-cage activity test, Y-maze test, fear conditioning test, and pre-pulse inhibition test (http://ja.brc.riken.jp/lab/jmc/mouse_clinic/en/business/pipeline.html). In the open-field test, Pcdh9-KO mice had a tendency to stay in the peripheral zone and to travel longer distances. In Crawley's three chamber test, Pcdh9-KO mice showed a tendency to avoid a novel object, although their social interaction with stranger mice was normal. In the home-cage activity test, activity of Pcdh9-KO mice was higher than that of wild-type mice during the light period. These results suggest that emotionality of the Pcdh9-KO mice was enhanced compared with wild-type mice. Taken together, we suggest that Pchd9 may be involved in neural functions underlying vestibular response and emotional behavior.

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Poster

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Title: Altered prefrontal anatomy and functional connectivity in mice lacking autism-associated gene Shank3

Authors: ***M. PAGANI**[1,2], C. ROBOL[1], R. GOMOLKA[1], A. LISKA[1,2], A. GALBUSERA[1], A. AKSIUTO[1], A. GOZZI[1]
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Abstract: Mutations in postsynaptic scaffolding protein Shank3 have been strongly implicated in 22q13 deletion syndrome (Phelan-McDermid syndrome) as well as other non-syndromic

forms of autism spectrum disorder (ASDs). A number of recent reports have investigated basal ganglia function in mouse lines harboring Shank3 mutations, revealing specific striatal circuit impairments underlying self-injurious repetitive grooming exhibited by these mutants. However, Shank3 mutations in humans are often associated with intellectual disability and cognitive impairments, suggesting that functional alteration in Shank3 could affect extra-striatal brain substrates such as high order cortical regions.
To probe this hypothesis, we used structural and functional MRI to obtain an unbiased mapping of cortical anatomy and connectivity in mice harboring Shank3B mutation ($Shank3B^{-/-}$). High resolution morpho-anatomical mapping using voxel based morphometry in Shank3B mutants revealed broad and prominent reductions in gray matter volume in prefrontal areas and lateral associative cortical regions of the mouse brain. In keeping with the gray matter reductions, regionally unbiased resting-state fMRI (rsfMRI) connectivity mapping revealed local and global connectivity reductions in prefrontal and anterior cingulate regions. This effect was associated with reduced long-range connectivity in midline integrative areas of the mouse default mode network. No overt genotype-dependent alterations in white macrostructure or fiber-organization were observed, as documented by DTI-based fractional anisotropy mapping, and tractographic analyses. We are currently performing prefrontal retrograde mapping to probe the role of altered mesoscale wiring in the observed functional connectivity alterations. Overall, our results suggest that Shank3 mutations can affect higher-order cortical activity via trophic and functional downregulation of prefrontal areas, and serve as a plausible neuro-functional correlate for the cognitive impairments observed in Shank3-associated ASD.

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Poster

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Swebilius Foundation

Title: A zebrafish model of epilepsy and autism spectrum disorders: Investigating the function of scn1lab

Authors: *C. SAKAI[1], F. ABBAS[1], S. IJAZ[1], M. GHOSH[2], J. RIHEL[2], E. J. HOFFMAN[1]
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Abstract: Human genetics studies have identified a number of genes that are strongly associated with both autism spectrum disorders (ASD) and epilepsy, including *SCN1A* and *SCN2A*. To gain insights into basic neurodevelopmental mechanisms involving these genes, we disrupted the function of the zebrafish paralog, *scn1lab*, which is 77% and 79% identical to *SCN1A* and *SCN2A*, respectively. Previously, we showed that zebrafish mutants of the ASD and epilepsy risk gene, *CNTNAP2*, display fewer forebrain GABAergic neurons, seizure sensitivity, and nighttime hyperactivity. Using pharmaco-behavioral profiling, we found that drugs with estrogenic activity rescue the *cntnap2* mutant behavioral phenotype. Here, we hypothesized that zebrafish *scn1lab* mutants might display similar phenotypes as *cntnap2* mutants. To test this, we generated two mutant lines lacking *scn1lab* function and performed structural and behavioral assays. These studies found that homozygous *scn1lab* mutants display a 25% reduction in brain area and a significant decrease in GABAergic neurons in the forebrain and hypothalamus compared to wildtype siblings [50% and 25% reduction, respectively, $p<0.0006$]. Homozygous mutants also display a 4-fold increased response to drug-induced seizures, consistent with attenuated GABAergic signaling. Further, using high-throughput behavioral profiling, we found that mutants display daytime hypoactivity and nighttime hyperactivity, in addition to altered responses to visual startle stimuli. Using pharamaco-behavioral profiling, we found that serotonin receptor antagonists, anticholinergic compounds, and adrenergic receptor agonists correlate with the mutant phenotype, and identified estrogens, nicotinic acetylcholine receptor agonists, and anti-inflammatory compounds as anti-correlating. These anti-correlating compounds may have the potential to rescue the mutant activity phenotypes, which we will test in future experiments. Together, these studies begin to identify common mechanistic pathways for further investigation in ASD and epilepsy.

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Poster

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Title: Multi-group cross-sectional study of a mouse model of TS reveals select neurobehavioral alterations for future preclinical studies

Authors: *S. SORIANO, S. HAO, S. VEERARAGAVAN, Z. WU, B. P. VICARI, C. S. WARD, J. TANG, R. C. SAMACO
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Abstract: Tuberous Sclerosis (TS) is a dominantly inherited genetic disorder caused by heterozygous mutations in either *TSC1* or *TSC2*, affecting multiple physiological systems. A spectrum of neurobehavioral features are highly prevalent in TS and include autism and impaired memory. Mouse models with mutations in either *Tsc1* or *Tsc2* have been reported to recapitulate features of TS, including impairments in behavior and cognition. Therapeutic intervention targeting the mTOR pathway holds great promise in improving the neurological symptoms associated with TS. However, in preparation for the possibility that mTOR inhibition is either incomplete or insufficient for therapeutic benefit, novel interventions independent of mTOR signaling must be identified. To this end, we focused our efforts on identifying the most robust and reproducible preclinical outcome measures in male and female mice lacking one copy of *Tsc2*. Our cross-sectional experimental design consisted of four cohorts tested at specific ages for select behavioral assays, in addition to an additional cohort of animals tested in a behavioral test battery. Moreover, given the recent concerns and issues related to the reproducibility of behavioral features in mouse models of ASD/IDD, our animals were tested across two different facilities by independent laboratories, and incorporating definitive ages and sexes ensured the rigor of these studies. The behavioral domain that is consistently altered in *Tsc2* mice across these studies and concordant with historical studies is abnormal aversive and spatial learning and memory. Furthermore, we confirmed that *Tsc2* mice displayed normal anxiety-like behavior, motor coordination, sociability and pain nociception, consistent with previous findings. *Tsc2* mice also demonstrated normal performance in several behavioral tests that have not been performed by other groups. In contrast, the single discrepant data that we found thus far was a female-specific difference in spontaneous exploratory activity uncovered by our groups compared with other published studies likely due to differences in factors such as age and methodology. Taken together, the results from these large-scale replication studies suggest that there is value in studying TSC2 deficiency to model select neurobehavioral features of the human condition that may serve as potential preclinical outcome measures but strengthen the need to further develop alternate approaches and/or models as useful *in vivo* tools to address the constellation of symptoms in TS.

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Poster

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Title: Development of a CRISPR-mediated molecular rescue of Pitt Hopkins Syndrome, a monogenetic autism spectrum disorder

Authors: B. MAYFIELD[1], J. F. BOHLEN[1], G. R. HAMERSKY[1], R. A. GALLO[1], *B. J. MAHER[1,2,3]
[1]Lieber Inst. For Brain Develop., Baltimore, MD; [2]The Solomon H. Snyder Dept. of Neurosci., [3]Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Pitt Hopkins Syndrome (PTHS) is a monogenetic autism spectrum disorder, resulting from various mutations to one copy of transcription factor 4 (TCF4). TCF4 is a basic helix-loop-helix transcription factor that has vital importance in neuronal migration and cortical development. While the exact molecular function and downstream effects of TCF4 are still largely unknown, the behavioral and medical deficits are clearly visible in patients having only a single copy of the gene. Here, we are attempting to use clustered regulatory interspaced short palindromic repeats (CRISPR) technology as a form of *in utero* gene therapy to encourage normal cortical development in a mouse model of PTHS. A CRISPR with dead Cas9 nuclease activity fused to a VP64 protein was shown to be effective at upregulating gene transcription (CRISPR/dCas9-VP64). We transfected mouse N2A cells and human HEK293 cells with CRISPR/dCas9-VP64 plasmid and tested a variety of guide RNAs (sgRNAs) that targeted different regions of the TCF4 promoter for efficacy in boosting TCF4 expression. We identified several sgRNAs that significantly increased expression of endogenous TCF4 transcript and protein. Next, we cloned the CRISPR/dCas9-VP64 construct and sgRNA into a single lentiviral vector. The effectiveness of this viral vector at boosting TCF4 expression is currently underway. Ultimately, we plan to test this viral vector for effectiveness at rescuing cellular and behavioral deficits observed in a mouse model of PTHS. We plan on performing *in utero* viral injection into the ventricles of developing mouse embryos (E12.5), a development timepoint just prior to the onset of TCF4 expression in the developing cortex.

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Poster

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Support: Hussman Foundation #15005

Title: Potential role of sema6A in autism spectrum disorder

Authors: K. V. MENZEL[1], *C. PLACHEZ[2]
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Abstract: During brain development, a multitude of neuronal networks form as neurons find their correct position within the brain and send out axons to synapse onto specific targets. Altered neuronal connectivity within these complex networks has been reported in Autism Spectrum Disorder (ASD), leading to alterations in brain function and multisensory integration. Semaphorins (also referred to as Semas), a large protein family of 20 members, have been shown to play an important role in neuronal circuit formation, and have been implicated in the etiology of ASD. This study focuses on the role of Sema6A, one of these family members, during brain development. Human studies have reported impaired thalamo-cortical connectivity in ASD (Nair et al. 2013), and Sema6A mutant mice display improper thalamo-cortical connections (Little et al., 2009). Moreover, ASD human brains display disorganized cerebellar granule cells (Wegiel et al., 2010; Blatt, 2012) and Sema6A has been shown to play a role in the migration of these granule cells (Kerjan et al., 2005). Taken together, these findings suggest that Sema6A may be an attractive candidate to study an underlying cause of ASD during brain development. Excitation/Inhibition balance is also affected in ASD (Hussman, 2001; Blatt et al., 2001; Gao and Penzes 2015), therefore, this study is investigating the contribution of Sema6A toward GABAergic interneuron migration during brain development. Our preliminary data demonstrates that Sema6A mutant mice display a reduction of parvalbumin immunostaining in the thalamus and cerebellum, whereas calbindin immunostaining is reduced in the hippocampus. These results suggest a potential role of Sema6A in interneuron migration during brain formation. The present study will further investigate how the loss of Sema6A could impact the formation of neuronal networks.

Disclosures: K.V. Menzel: None. **C. Plachez:** None.

Poster

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Title: Deletion of the autism-related gene neurexin II (Nrxn2) causes alterations to the structure of the social brain as measured by DT-MRI and CLARITY

Authors: *J. DACHTLER[1], E. PERVOLARAKI[2], A. TYSON[3], F. PIBIRI[1], R. J. RODGERS[2], C. LEVER[1], S. J. CLAPCOTE[2], L. ANDREAE[3]
[1]Durham Univ., Durham, United Kingdom; [2]Univ. of Leeds, Leeds, United Kingdom; [3]King's Col. London, London, United Kingdom

Abstract: It is becomingly clear that many of the genetic mutations thought to be implicated in autism cluster upon proteins relating to synaptic signaling. A family of presynaptic proteins that have garnered recent interest have been the neurexins (NRXNs). Neurexins are encoded by three genes (*NRXN1, 2* and *3*) and convey a functional role in GABAergic and glutamatergic synaptic transmission. Given the reports of *NRXN2* deletions in autism, we recently studied a mouse model that lacked αNrxn2 to provide causal evidence that the loss of Nrxn2 resulted in ASD-like behaviors. We found that social approach and social recognition was impaired in mice with a homozygous deletion (KOs) of αNrxn2. To explore whether the loss of αNrxn2 changes the microstructure of brain regions associated with social behavior, we scanned fixed brains of wild-type (n=6) and αNrxn2 KO (n=6) mice in a 9.4T spectrometer using a diffusion tensor MRI (DT-MRI) protocol (TE: 35 ms, TR: 700 ms, 12 signal averages). The ex vivo mouse brain 3D diffusion-weighted images were then analyzed for fractional anisotropy (FA), apparent diffusion coefficient (ADC), radial diffusion (RD) and axial diffusion (AD). Our analysis focused upon the hippocampus, amygdala, anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC). We also examined diffusion properties of tracts between the amygdala and hippocampus, and amygdala and orbitofrontal cortex. The same ex vivo brains were then sectioned focusing on the same brain regions and were cleared using the CLARITY procedure. Sections were stained for neurofilament and DAPI and imaged by confocal microscopy. Cell nuclei and fibres were segmented, and for each ROI, cell density, fibre density and anisotropy index were calculated.

We report that the loss of αNrxn2 causes FA changes to the anterior (p=0.037), posterior (p=0.007) and basolateral amygdala (p=0.031), as measured by DT-MRI. The ADC of the dentate gyrus of the anterior (p=0.002) and posterior (p<0.0001) hippocampus was increased. The OFC had significantly increased AD (p=0.008) and RD (p=0.002). We also found significantly increased RD of OFC to amygdala tracts (p=0.0005). Using the same tissue, cell counting from CLARITY-treated tissue revealed no significant cell density differences from any brain region tested. However, neurofilament staining found significant increases to anisotropy index in the amygdala (p=0.02), orbitofrontal cortex (p=0.04) and the ACC (p=0.003). These results suggest that deletion of αNrxn2 causes discrete changes to the microstructure of the social brain that can be detected by both DT-MRI and CLARITY without gross morphological changes to cell density.

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Poster

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Title: The architecture and development of the axon initial segment (AIS) in an autistic mouse model

Authors: *M. A. ALSHAMMARI[1], M. R. KHAN[1], K. A. ALHOSAINI[1], R. ALI[2], M. BOUDJELAL[2], T. K. ALSHAMMARI[1]
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Abstract: The axon initial segment (AIS), a specific region for action potential initiation in neurons, is a critical determinant of neuronal excitability. Growing evidence indicates that the appropriate recruitment of the AIS macrocomplex is essential for synchronized firing. However, any disruption of the AIS structure is linked to the etiology of multiple disorders, including autism spectrum disorder (ASD), a disease characterized by deficits in social communication, stereotyped behaviors, and very limited interest. Until now, a complete understanding of the molecular elements that lie at the basis of AIS in ASD has remained elusive. Here, we examine the AIS structure at different developmental time points in the BTBR T+ Itpr3tf/J mouse model, a valid model that exhibits behavioral, electrical, and molecular features of autism, compare to the C57/B6 wild-type control mouse. By using Western blot studies and high-resolution confocal

microscopy, our data suggest a disruption of the expression of AIS markers such as ankyrin-G and fibroblast growth factor 14 (FGF14) in BTBR compare to the wild-type control mice. Ongoing studies are evaluating the impact of inositol 1,4,5-trisphosphate receptors 3 (IP3R), a critical receptor for maintaining calcium homeostasis in neurons, in the functional integration of voltage-gated sodium channel Nav1.6 in the cortical pyramidal neurons of BTBR mice at different developmental time points. Our results may provide evidence of previously undescribed mechanisms that play a role in the pathogenesis of ASD.

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Brain Canada

Title: Mouse Models show that Cerebellar Networks are altered in Autism

Authors: *J. ELLEGOOD[1], Y. YEE[1], R. HENKELMAN[1], P. TSAI[2], J. P. LERCH[1]
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Abstract: Background - Over the past 7 years, we have established a large cohort of mouse models related to autism. This allows for investigation of a large autism population in the mouse, which can be also viewed as representative of idiopathic autism. Therefore, differences in networks or regions across autism can be determined. The cerebellum has been frequently found to be different in autism and autism related disorders (see reviews by Tsai, 2016, Hampson and Blatt 2015, and D'Mello and Stoodley 2015), so the question we asked was: Can we detect cerebellar differences across our model autistic population? **Objectives** - To assess differences in the cerebellum and cerebellar networks across multiple autism mouse-lines to determine any commonalties or differences shared across the population. **Methods** - The data used in this study was accumulated from 44 different autism mouse-lines and included greater than 60 genotypes and over 1500 mice. *MRI Acquisition* - A multi-channel 7.0 Tesla MRI was used to acquire anatomical images of the brain. A T2-weighted, 3-D fast spin-echo sequence was used that yielded an image with 56 μm isotropic voxels (3D pixel) in ~14 h. *Data Analysis* - To visualize and compare any differences the images are registered together. The goal of the registration is to

model how the deformation fields relate to genotype, wild-type (WT) vs. autism mutant (Lerch et al., 2008). Volume differences are then calculated across the cerebellum in individual voxels or for 39 different cerebellar regions and their corresponding network (Steadman et al. 2014). **Results** - Overall, the cerebellum as a whole was one of the most affected regions across the brain (Ellegood et al. 2015). In addition to the cerebellum as whole, we examined the cerebellar cortex, hemispheres, vermis, and deep cerebellar nuclei (DCN). Out of those five regions only the DCN, the outputs of the cerebellum, were significantly smaller in the autism group (t-value of -4.26). Therefore, we further examined the projections from the DCN using anatomical covariance to assess the structural connectivity (Evans, 2013). The connectivity was measured between the DCN and the cerebellar cortex, thalamus, pontine nucleus, and the cortex, and was altered only between the DCN and cortex in the autism models when compared to the WT. **Conclusions** - Using anatomical covariance to assess structural connectivity in the mouse models of autism has revealed an alteration in the connectivity between the DCN and the cortex. This alteration preferentially affects the somatosensory, visual and association corticies. Further investigation is warranted to determine the underlying cause of this difference.

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Poster

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Brain and Behavior Foundation

Title: Characterization of ankyrin mutations associated with autism spectrum disorder

Authors: *J. GARZA[1], T. L. PETRYSHEN[2]
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Abstract: Recent large-scale genomic studies have identified candidate genes involved in synaptic transmission that are highly associated with autism spectrum disorder (ASD), including ANK2 and ANK3. Loss of function missense mutations were associated with autistic patients. The goal of this project is to functionally characterize de novo loss of function mutations in ankyrins and identify their contribution to ASD. A CRISPR/Cas9-based approach was used to transcriptionally repress ankyrin in a cell model. Fourteen sgRNA and one non-targeting control

sgRNA were designed and screened for efficiency of transcriptional repression. Ankyrin levels were measured by qPCR. Tubulin polymerization and end-binding protein 3 expression were evaluated using Western blot. Furthermore, CRISPR/Cas9 was also used to induce point mutations within the Ank2 gene. Fourteen sgRNA were designed upstream of the transcriptional start site of Ank3. Four sgRNA transcriptionally repressed Ank3b, however three of these had off-target effects whereas a single sgRNA had specificity for Ank3b. The expression of Ank3b was reduced to approximately half of control levels after CRISPR-mediated repression. As a result of Ank3 repression, tubulin polymerization was impaired, suggesting that microtubules were destabilized. The protein expression of end-binding protein 3 (EB3) was evaluated after transcriptional repression of Ank3 and resulted in a significant increase in EB3 levels. These results indicate transcriptional repression of ankyrin destabilizes microtubules which induces neuronal dysfunction that may be associated with ASD. These data will provide a better understanding of the genetic factors underlying ASD.

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Poster

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Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Wellcome Trust DBT India Alliance, DBT and DST (VT)

NCBS Career Development Fellowship (IK)

CSIR-UGC (UJ)

Title: An autism-susceptibility candidate gene controls variability of escape responses in larval zebrafish

Authors: *U. JHA[1], I. KONDRYCHYN[1], V. KORZH[2], V. THIRUMALAI[1]
[1]Natl. Ctr. For Biol. Sci., Bangalore, India; [2]Intl. Inst. of Mol. and Cell Biology,, Warsaw, Poland

Abstract: The autism susceptibility candidate 2 gene (AUTS2) is associated with multiple neurological disorders including autism spectrum disorders and intellectual disabilities. However, apart from a few findings suggestive of a regulatory role, the function of this gene remains unknown. We set out to determine the function of auts2 in neural development and circuit function using larval zebrafish (*Danio rerio*). We identified four auts2 paralogs in zebrafish: auts2a, auts2b, fbrsl1 and fbrs. Of these, auts2a is located on chromosome 10 and codes for a protein with 1278 amino acids residues. Expression of auts2a was seen widely in the

central nervous system with prominent expression in the hindbrain. At 14 hours post fertilization (hpf), auts2a is strongly expressed in rhombomere 4 - the place where Mauthner neurons, that trigger escape response, are located.
To test the function of auts2a in neural circuit assembly, we induced mutations in the auts2a locus using transcription activator-like effector nucleases (TALEN). We isolated several alleles with loss of function due to frame-shift mutations leading to premature stop codons. Mutant fish showed normal gross morphology and development and were fertile. Escape response is critical for survival, is stereotyped, and the underlying circuit is well-characterised. Therefore, we evaluated escape response in auts2a mutants as a tool for investigating the role of auts2a in circuit development and behavior. The latency to trigger an escape response was longer in auts2a mutants compared to wildtype. Further, the variability of latency was also higher compared to the tightly regulated short latencies in wild type fish and heterozygotes. We also observed greater proportions of no response trials and ipsilateral responses in auts2a mutants compared to wild type fish and heterozygotes. Lastly, these defects were exacerbated when stimuli were applied to the tail than in trials when the stimuli were applied to the head, hinting at defects in Mauthner neurons. Our next steps focus on looking at calcium activity profile of Mauthner and its homolog to get mechanistic insights into these behavioural defects. Our study on auts2 genes may further reveal general principles in how variability, a fundamental aspect of behavior, arises.

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Title: FOXG1 overexpression and epigenetic landscape in a human iPSC-derived forebrain organoid model of severe, macrocephalic autism spectrum disorder

Authors: *N. NOLAN[1], J. MARIANI[1], F. WU[1], A. ABYZOV[3], F. M. VACCARINO[1,2]
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Abstract: Autism Spectrum Disorder (ASD) is a highly heritable developmental disorder which, in severe cases, is associated with cortical overgrowth, macrocephaly, and excitatory/inhibitory neuronal imbalance. Using an organoid model of forebrain development, we previously

implicated FOXG1, a transcription factor involved in early forebrain patterning, in contributing to the ASD phenotype in four families of macrocephalic ASD patients with no known ASD-associated mutations (Mariani et al., Cell 2015). This phenotype included a transient increase in cell proliferation, overproduction of GABAergic neurons, and neurite/synaptic overgrowth. RNA-seq studies and gene network analyses also showed that FOXG1 is upregulated as well as co- expressed with other transcription factors and cell fate determinants in ASD patients' forebrain organoids. Increased FOXG1 activity may explain some features of ASD pathophysiology, fitting with FOXG1's known role in cortical growth and GABAergic neuronal development. We showed that FOXG1 shRNA knockdown normalized both expression of several GABAergic neuron-associated genes and GABAergic neuron overproduction in ASD-derived organoids. However, to what extent FOXG1 upregulation is sufficient to generate the ASD organoid phenotype, and the details of the FOXG1 regulatory network in health and disease, remain unclear. Furthermore, the epigenetic landscape of ASD is not well understood, particularly in regard to FOXG1. ASD-derived organoids show increased FOXG1 expression but without mutations in the FOXG1 sequence or upstream promoter regions, suggesting that epigenetic or distal regulatory changes might contribute to FOXG1 overexpression. To answer these, we use an inducible system to overexpress FOXG1 in wild-type organoids from ASD patients' fathers and unrelated, age-matched controls. Comparisons using RNA-seq, ChIP- seq, immunocytochemistry, and neuronal phenotype analyses are used to examine the extent to which FOXG1 overexpression alone recapitulates the ASD transcriptomic and neurophenotypic changes seen in organoids derived from ASD probands. Second, by performing histone ChIP-seq analyses on organoids derived from ASD patients and their unaffected fathers at time points corresponding with early forebrain development, and then intersecting these regulatory regions with gene variants associated with ASD in large cohorts of families (from MISSNG and SFARI datasets), we explore the dynamic developmental epigenetic landscape of our ASD cohort, including potential genetic and/or epigenetic causes for the previously detected transcriptome alterations such as the overexpression of FOXG1.

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Poster

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Title: Fc receptors: Critical regulators of central nervous system (CNS) delivery and distribution of antibodies

Authors: *G. NEHRA[1], N. N. KUMAR[1], M. E. PIZZO[1,2], B. WILKEN-RESMAN[1], G. GREENE[1], S. BOROUMAND[1], K. VANG[3], R. G. THORNE[1,2,4,5]
[1]Pharmaceut. Sci. Div. (School of Pharmacy), [2]Clin. Neuroengineering Training Program, [3]Neurobio. Major, Col. of Letters and Sci., [4]The Ctr. for Neurosci. and Neurosci. Training Program, [5]Cell. and Mol. Pathology Grad. Program, Univ. of Wisconsin-Madison, Madison, WI

Abstract: With antibody-based therapeutics emerging as a promising treatment for central nervous system (CNS) disorders, characterizing antibody distribution in the brain microenvironment will be critical for successful translation. Immunoglobulin G (IgG) antibody distribution is expected to be influenced by binding to a variety of endogenous Fc receptors. Fc receptors, present on immune and non-immune cells, bind to the crystallizable fragment (Fc region) of immunoglobulins throughout the body. Surprisingly, the expression of these receptors in the CNS has not been well described. Here, we have used immunohistochemistry to investigate the distribution of two Fc receptors in the brain - the inhibitory Fc gamma receptor (FcγRIIb) and the neonatal Fc receptor (FcRn). The expression of these receptors was studied at the nasal epithelia (olfactory and respiratory), trigeminal nerve, lymph nodes, brain, dura and spinal cord. FcγRIIb is an inhibitory receptor that binds to IgG with low affinity ($K_d \sim 10^{-6}$ M). We observed that FcγRIIb expression was relatively high at the cerebrospinal fluid (CSF) - brain interfaces. Immunoreactivity co-localized with surface astrocytes and also possibly leptomeningeal cells. Intriguingly, the distribution of centrally applied (intranasal or intrathecal administration) IgG appears to be restricted at locations with high FcγRIIb expression, suggesting that reversible binding may be limiting CNS distribution of IgG. The neonatal Fc receptor (FcRn) only binds IgG with high affinity in slightly acidic environments (pH ~ 6.5) such as endosomes/lysosomes and mucus layers overlying certain epithelia, with much weaker binding affinity in most other physiological compartments (pH ~ 7.4), e.g., blood and CSF. In the brain microenvironment, FcRn appears to be expressed by brain endothelial cells and has been thought to play some role in the clearance of IgG from the brain. Our data suggests that FcRn is prominently expressed by cells around the perivascular space and the sub-arachnoid space as well as at CSF-facing interfaces (e.g., ventricular surfaces, choroid plexus epithelial cells and their associated stroma). We also observe FcRn expression in the olfactory epithelia. We hypothesize that FcRn binding may be an important influence on the uptake and transport of IgG administered via the CSF or intranasally. Overall, our findings may potentially inform the engineering of antibody therapeutics for more efficient distribution within the CNS as well as

provide new insights into the physiological factors influencing the distribution of endogenous IgG.

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Poster

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SC CTSI (NIH/NCATS) through Grant UL1TR000130

Title: Increasing selective hip-knee control of infants at high risk for cerebral palsy: A feasibility study

Authors: *B. A. SARGENT, K. HAVENS, N. MARCIONE, C. J. WINSTEIN, L. FETTERS
USC, Los Angeles, CA

Abstract: Background. Infants with brain insults are at high risk for cerebral palsy (HRCP) and have reduced selective hip-knee control. We developed an in-home intervention to encourage selective hip-knee control that uses a Microsoft Kinect to track an infant's leg movements and activate an overhead infant mobile based on specific kicking actions. The purpose of this study is to determine: (1) the feasibility of the in-home mobile intervention, (2) if infants at HRCP and infants with typical development (TD) learn the contingency between leg movement and mobile activation, (3) if both groups increase selective hip-knee control when activating the mobile compared to spontaneous kicking. **Methods**. Six infants at HRCP and 12 infants with TD at 3½-months corrected-age participated in the study. Each infant participated in an 8-10 min/day, 5 day/week, 6-week mobile intervention. On the first day of each week, the spontaneous kicks of each infant were assessed for 2-min, followed by 8-min of the infant playing with a mobile that activated based on specific kicking actions. For the next 4 days, the infant played with the mobile for 8-min each day. At the end of 6-weeks, parents answered questions about feasibility.

Learning was assessed weekly based on an increase in the proportion of time that the infant demonstrated the reinforced leg actions (RLA) when playing with the mobile compared to spontaneous kicking. Selective hip-knee control was assessed weekly based on a decrease in the hip-knee correlation coefficient (CC) of kicks that activated the mobile compared to spontaneous kicking. **Results**. Feasibility: Parents stated infants were happy during the majority of sessions and the in-home intervention was easy to implement. Adherence was 93-100%. Learning: All infants learned that their leg action activated the mobile: infants with TD met the individual learning criteria for a median of 5 weeks (range 3-6), and infants at HRCP met the criteria for a median of 3 weeks (range 2-4). For 4 of 6 weeks, the group with TD demonstrated a significant increase in RLA when activating the mobile (21.4±1.3%) compared to spontaneous kicking (9.8±2.0%, $p<0.0001$). Selective hip-knee control: For 5 of 6 weeks, the group with TD demonstrated a significant decrease in hip-knee CC when activating the mobile (0.32±0.08) compared to spontaneous kicking (0.59±0.08, $p<0.0001$). **Conclusions/Significance**. The mobile intervention is feasible. Preliminary data supports that infants with TD and HRCP are learning that their leg actions activate the mobile, and infants with TD demonstrate more selective hip-knee control when activating the mobile compared to spontaneous kicking.

Disclosures: B.A. Sargent: None. **K. Havens:** None. **N. Marcione:** None. **C.J. Winstein:** None. **L. Fetters:** None.

Poster

651. Modeling Neurodevelopmental Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 651.28/B59

Topic: A.01. Neurogenesis and Gliogenesis

Support: Adrian Tinsley Program Grant Program, Office of Undergraduate Research, Bridgewater State University

Title: ERK-mediated phosphorylation of Egr1-3 coregulator NAB2 at multiple sites

Authors: K. M. ABT[1], N. A. BERRY[1], S. KLETSOV[1], T. T. EDWARDS-GRANT[1], J. W. TULLAI[2], *K. W. ADAMS[1]
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Abstract: The early growth response (Egr) family of transcription factors comprises five members, Egr1-4 and Wilms Tumor 1 (WT1), which play roles in various cell behaviors including proliferation, apoptosis, and differentiation in a cell type- and stimulus-specific manner. Roles for Egr1-3 are particularly well-documented in the nervous system. Egr1 and 3 contribute to learning and memory through regulation of genes that mediate synaptic plasticity and long-term potentiation. Egr2 controls hindbrain development through regulation of *Hox* gene

expression and drives peripheral nerve myelination through, at least in part, activation of the gene encoding myelin protein zero in Schwann cells. Egr1 and 2 also contribute to transcriptional network that drives neuronal differentiation of PC12 cells. However, the mechanisms that regulate Egr1-3 activities in the nervous system are not fully understood. One mechanism of regulation involves protein-protein interactions with co-regulators NAB1 and 2 through a conserved R1 domain in Egr1-3. Most reports demonstrate that NABs repress Egr1-3 transactivation activity when bound, however, NABs can also enhance transactivation in a target gene-specific manner. The mechanisms controlling the effect of NABs on Egr activities are not clear. Here, we provide evidence that NAB2 regulation may involve its phosphorylation at several sites by ERK. Using PC12 cells as a model system, our data demonstrate that nerve growth factor (NGF) induces a NAB2 mobility shift in SDS-PAGE within 10 minutes of treatment. The mobility shift was reversed when lysates from NGF-treated cells were treated with lambda phosphatase, suggesting the shift is due to phosphorylation. Inhibition of ERK signaling during NGF treatment blocked the mobility shift, while recombinant ERK phosphorylated recombinant NAB2 in an *in vitro* kinase assay, together indicating that direct phosphorylation of NAB2 by ERK may be responsible for the NAB2 mobility shift in response to NGF. Nine potential ERK phosphorylation sites were identified in NAB2, which were mutated individually to alanine within a NAB2 expression construct to evaluate phosphorylation at those sites based on their mobility in SDS-PAGE. Of the nine mutants, three exhibited clear changes in NAB2 mobility, which were additive in double and triple mutants for those sites. Ongoing experiments are evaluating the effect of NAB2 phosphorylation on its localization and regulation of Egr1-3.

Disclosures: K.M. Abt: None. **N.A. Berry:** None. **S. Kletsov:** None. **T.T. Edwards-Grant:** None. **J.W. Tullai:** None. **K.W. Adams:** None.

Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.01/B60

Topic: A.07. Developmental Disorders

Support: R01 MH101209

Title: Atypical postnatal development of feedback excitatory and local inhibitory circuits in layer I of prefrontal cortices in autism

Authors: *I. TRUTZER[1], B. ZIKOPOULOS[2]
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Abstract: Layer I of the cortex appears early in development and is composed of glia and limited neurons dispersed among dendrites and axons. The neurons in layer I direct the patterning of cortical lamination in mammals, including humans. In adulthood, layer I contains few, overwhelmingly inhibitory, neurons. Dendrites of excitatory pyramidal neurons from the deep cortical layers terminate in this layer, where they receive synapses from feedback projections that modulate cortical function. The balance of excitation-inhibition in this layer is therefore integral for proper cortical information processing. Despite the unique role of layer I, little is known about the postnatal development of this layer. In order to study the excitatory-inhibitory balance in this layer through postnatal development, we studied the distribution of distinct classes of inhibitory neurons and the density of myelinated axons in layer I of prefrontal cortices in typically developing children and adolescents. We compared our findings with data from children and adolescents with autism, a disorder characterized by an imbalance in excitation and inhibition in the brain. Inhibitory neurons are categorized by their expression of calcium binding proteins. Neurons that express calretinin (CR) and calbindin (CB) exert modulatory inhibition on their targets, while those that express parvalbumin (PV) are strongly inhibitory. CR-expressing neurons have been observed in layer I in prenatal and adult tissue. Neurons expressing CB and PV are not present in layer I in the neurotypical adult brain. We report that in addition to CR-expressing neurons, PV- and CB-expressing neurons are found in layer I of PFC in neurotypical children and adolescents. In autism, children and adults have CB, PV, and CR-expressing neurons in layer I in LPFC and ACC. In LPFC, children with autism have a sharp reduction in the density of dis-inhibitory CR-expressing neurons during adolescence. In this same region, children with autism have a steeper increase in the proportion of small axons, representative of short-range pathways, compared with neurotypical children. In ACC, children with autism have increased density of PV-expressing neurons in adolescence relative to neurotypical children; feedback pathways in this area are heterogeneous, in line with the widespread connectivity of this area. The observed changes in cortical structure, including the appearance of strongly inhibitory PV neurons in layer I and reduction of dis-inhibitory CR-expressing neurons in adolescence, along with changes in feedback excitatory pathways, likely have significant implications for the efficiency of cortical processing in these areas.

Disclosures: I. Trutzer: None. **B. Zikopoulos:** None.

Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.02/B61

Topic: A.07. Developmental Disorders

Support: R01 MH101209

R01 NS024760

Title: Common laminar distribution and density of synapses and axons in prefrontal cortices in humans and non-human primates

Authors: *M. GARCIA-CABEZAS[1], I. TRUTZER[2], H. BARBAS[3], B. ZIKOPOULOS[3]
[1]Hlth. Sci. (Neural Systems Lab), Sargent College, Boston Univ., Boston, MA; [2]Neurosci., [3]Boston Univ., Boston, MA

Abstract: The anterior cingulate cortex (ACC) and lateral prefrontal cortex (LPFC) communicate in a prefrontal attention network in humans. The coordinated activity of these cortices is necessary for switching attention, and may be involved in decision making and encoding of emotional responses. Excitatory synaptic connections between ACC and LPFC have been characterized in rhesus macaques, where axons from ACC mainly target the upper layers (1, 2, and upper 3) of LPFC, which is typical of feedback pathways, while axons from LPFC mainly target the middle layers (lower 3 through upper 5) of ACC, typical of feedforward pathways. Disruption of connections and local signal processing of ACC and LPFC could lead to behavioral symptoms of attentional regulation, seen in disorders such as autism spectrum disorders (ASD). Studies have characterized the structure of long- and short-range pathways in the white matter to characterize structural connectivity between brain regions. In order to expand on these analyses, it is necessary to study the intercortical structure of connected brain areas to identify possible changes in the distributions of axons or synapses that could represent changes in specific classes of pathways. We quantitatively analyzed the density of synapses and axons in the individual cortical layers of these two areas in adult rhesus macaque brains, and compared the results with the laminar density of myelinated axons in adult humans. The relative density of each synapse type differs between the different cortical layers and areas, and influences the regulation of specific types of pathways. We also correlated the axon density of different cortical layers in rhesus macaque and human brain tissue with the goal to determine if the rhesus monkey can be used as a primate model system. We determined that the density of axons is highest in the deep cortical layers and lowest in Layer II, while synapse density shows the opposite trend. ACC (area 32) has fewer myelinated axons, especially in the deep layers, and a higher density of synapses in adult monkeys when compared to LPFC (area 46). The densities of axons in the different cortical layers follow similar trends in rhesus and human subjects. These findings serve as a basis to understand important developmental processes that influence neural circuit structure.

Disclosures: M. Garcia-Cabezas: None. **I. Trutzer:** None. **H. Barbas:** None. **B. Zikopoulos:** None.

Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

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Program#/Poster#: 652.03/B62

Topic: A.07. Developmental Disorders

Support: IMI, EU-AIMS, grant 115300

Italian Min. Health, grant NET-2013-02355263

Title: ITGB3 gene promoter variants influence 5-HT blood levels by modulating the externalization of the platelet 5-HT transporter in Autism Spectrum Disorder

Authors: *A. M. PERSICO[1,2], S. GABRIELE[3], M. CANALI[3], C. LINTAS[3], R. SACCO[3], C. GREGORJ[3]
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Abstract: Genetic factors contribute significantly to autism spectrum disorder (ASD). The *ITGB3* gene, located on human chr. 17q21.32, encodes integrin beta 3, the beta subunit of the platelet membrane adhesive protein receptor complex GPIIb/IIIa. Integrin beta 3 interacts with the serotonin transporter (SERT), encoded by the *SLC6A4* gene, regulating its trafficking on the plasma membrane of platelets and serotonin (5-HT) uptake in synapses. *ITGB3* and *SLC6A4* were both identified as quantitative trait loci (QTLs) for 5-HT blood levels, known to be elevated in 20-30% of ASD patients (Gabriele et al., Eur Neuropsychopharmacol 24:919, 2014). The *rs2317385* G allele in the *ITGB3* promoter region is significant associated with 5-HT blood levels in 293 Italian ASD families (Napolioni et al., Eur J Hum Genet 19:353, 2011). To identify functional *ITGB3* variants contributing to elevate 5-HT blood levels, we sequenced the *ITGB3* promoter region, exons and exon-intron junctions in twenty individuals selected on the basis of known genotypes. Six SNPs were identified, all located in the *ITGB3* promoter region and in tight linkage disequilibrium with *rs2317385*, defining four haplotypes. Each haplotype was cloned into pGL4.10, transfected into hematopoietic (K-562 and HEL 92.1.7) and neuronal (N2A) cell lines, and analyzed by luciferase assay. A significant increase in *ITGB3* promoter activity and differential allelic effects were detected after differentiation into megakaryocytes both in K-562 and HEL 92.1.7, but not in N2A cell lines, with the *rs55827077* C allele associated with greater luciferase activity ($P<0.05$), as predicted. This same allele was associated with elevated 5-HT blood levels in 176 ASD patients ($P=0.01$), with significantly greater amounts of platelet integrin beta 3, as assessed by western blotting ($P=0.02$), and with increased SERT externalization on the platelet plasma membrane ($P=4.05 \times 10^{-11}$). These results support cell type- and differentiation-specific effects of *ITGB3* promoter activity exerted by common genetic variants linked to hyperserotoninemia in autism.

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Poster

652. Autism: Synapses and Circuits

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Program#/Poster#: 652.04/B63

Topic: A.07. Developmental Disorders

Support: NIMH F31 MH111147

NIMH T32 MH096678

NIH DP2 MH100012-01

NIA T32 AG049688-02

Title: Key role of BET-controlled gene networks in autism

Authors: *J. SULLIVAN[1], A. BADIMON[1], P. AYATA[1], U. SCHAEFER[2], M. DUFF[1], R. K. PRINJHA[3], A. SCHAEFER[1]
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Abstract: Autism Spectrum Disorder (ASD) is a group of complex neurodevelopmental disorders that are characterized by social impairment and repetitive behaviors. There is no known single cause for ASD, but it is clear that there are strong genetic and environmental components to the development of the disorder. Recent whole-exome sequencing studies confirmed synaptic dysfunction as a central mechanism in the disease pathology but also surprisingly implicated a group of transcriptional regulators. This suggests the possibility of a novel, epigenetic mechanism underlying ASD where disruptions in gene transcription lead to abnormal neuronal development and circuit formation. To address the contribution of transcriptional dysregulation as the cause of ASD-like phenotypes, we used a novel pharmacological approach to temporarily inhibit transcription during postnatal brain development. In collaboration with GlaxoSmithKline, we developed a brain-permeable inhibitor, I-BET858, of the bromodomain and extraterminal domain-containing proteins (BETs) which regulate the elongation phase of transcription. We found a surprisingly selective impact of BET inhibition on synaptic functional genes. These I-BET858-sensitive genes are characterized by their extended length which may explain their selective sensitivity. Many of the I-BET858-sensitive genes have also been linked to ASD in humans, suggesting the key role of the BET-controlled gene network in the disorder. Finally, we found that pharmacological inhibition of BET-dependent transcription during postnatal brain development led to the development of an autism-like phenotype in mice. These findings

illustrate that transcriptional dysregulation can directly impair brain development, supporting the existence of an epigenetic mechanism underlying Autism Spectrum Disorder.

Disclosures: **J. Sullivan:** None. **A. Badimon:** None. **P. Ayata:** None. **U. Schaefer:** None. **M. Duff:** None. **R.K. Prinjha:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **A. Schaefer:** None.

Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.05/B64

Topic: A.07. Developmental Disorders

Support: NYU Challenge Grant 2016-17

Title: Serotonergic axons appose angiogenic blood vessels in autism temporal cortex: An immunocytochemical study in postmortem human brains

Authors: *K. N. MANGAR, E. C. AZMITIA, X. F. JIA
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Abstract: Serotonin (5-HT) axons have long been associated with the normal brain vasculature. Increased serotonin axons (Azmitia et al., 2011b) and increased angiogenic blood vessels (Azmitia et al., 2016) have been demonstrated in the autism brain. Studies also showed that increasing brain 5-HT with serotonin specific reuptake inhibitors (SSRIs) results in hippocampal angiogenesis in rats (Warner-Schmidt and Duman, 2007) and in humans (Boldrini et al., 2012). Additionally, 5-HT is a crucial driving force of tumor angiogenesis (Zamani and Qu, 2012; Qin et al., 2013). In this study, we focused on 5-HT transporter-immunoreactive (5-HTT-IR) axons and nestin-IR proliferating pericytes on blood vessels to explore for an anatomical association between these axons and blood vessels in the autism brain. The present work used postmortem brain tissues from 3 age groups of ASD donors (2.8 - 10 years; 10.1 - 20 years; 20.1 - 29 years) and their age matched controls (2.1 - 30 years). Brain hemispheric sections of the temporal cortex were labeled with mouse monoclonal nestin (Millipore), a marker of proliferating blood vessels; rabbit polyclonal Ulex Europaeus Agglutinin 1(UEA-1) lectin, a marker of mature blood vessels, (Vector Laboratories, CA); and mouse monoclonal serotonin transporter (5-HTT) (MAb Technologies, GA), a marker of serotonin axons. These primary antibodies were used in single and double immunocytochemistry. Double immunolabeling with UEA-1 and 5-HTT confirmed prior observations of serotonin axons innervating mature endothelial cells in normal brains**.** This relationship is also present in autism brains of all ages. Double labeling with nestin and 5-HTT in autism brains showed extensive labeling of 5-HTT-IR axons on blood vessels covered with nestin positive proliferating pericytes throughout the temporal cortex. Many axons were seen

contacting proliferating pericytes all along the entire blood vessel. This strong interaction was visible in all 3 age groups. However, the 5-HTT-nestin relationship was not observed in control brains as nestin expression is high only in early development (<2 years) and in angiogenic vessels but not in mature vessels of normal brains. This close apposition of 5-HTT-IR axons to nestin-IR positive pericytes illustrates a crucial association in the angiogenic autism brain further suggesting that 5-HT contact may drive angiogenesis and pericyte proliferation in autism patients. This could be a new therapeutic target for drug intervention in autism patients by blocking the 5-HT pathway.

Disclosures: K.N. Mangar: None. **E.C. Azmitia:** None. **X.F. Jia:** None.

Poster

652. Autism: Synapses and Circuits

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.06/B65

Topic: A.07. Developmental Disorders

Support: Hussman Foundation grant #HIAS15006

Title: Segregated expressions of autism risk genes Cdh 9 and Cdh 11 in autism-relevant regions of developing cerebellum

Authors: *C.-L. WANG[1], Y. WANG[1], X. YUAN[2]
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Abstract: Recent genome wide association studies (GWAS) and whole genome sequencing (WGS) have highlighted type II cadherins as risk genes for Autism Spectrum Conditions (ASC). To understand how these cadherins may be linked to the morphogenesis of autism-relevant brain regions, we carried out *in situ* hybridization (ISH) to examine the mRNA expression profiles of two autism-associated genes Cdh9 and Cdh11 in developing mouse brains. We found that during the first postnatal week both genes are expressed at a high level but in distinct sub-populations of Purkinje cells of the cerebellum, a frequently targeted area in autism. As development proceeded, the expression of Cdh9 and Cdh11 both declined and maintained at a low level in adulthood in the mouse brain. Interestingly, developmental expression of Cdh11 was largely confined to areas that mediate high cognitive functions of the cerebellum in the adult, including the dorsal lobules of the vermis and the lateral hemisphere equivalent to the Crus I and Crus II areas in human, and these areas are known to be highly vulnerable in ASC. Careful examination of adjacent sagittal sections showed that the two genes are expressed largely in a complementary pattern with sharp boundaries. In particular, in the lobules 6/7 of the vermis, Cdh11 expressing area was confined to the central part, flanked by the Cdh9 expressed area. The Purkinje cell marker calbindin also exhibited differential expression in an area-specific manner. Interestingly, the high Cdh11

expression in the central part of the lobe 6/7 was associated with a very low expression of calbindin in the same area, whereas in the flanking area of high Cdh9 expression, calbindin was expressed at a much higher level. In lateral area of the cerebellar hemisphere, a similar segregated expression pattern of Cdh9 and Cdh11 was observed, also with an inverse correlation between the expression of Cdh11 and calbindin. Our results revealed a clear segregation of two autism risk genes Cdh9 and Cdh11 with regard to their expression in Purkinje cells, raising the possibility that these two genes may exert different but correlated functions in orchestrating the postnatal development of cerebellar circuitries that are closely relevant to cognitive functions. Importantly, the very low calbindin level in the Cdh11-high domains suggests that Cdh11 may regulate the delayed maturation of Purkinje cells in areas associated with cognitive functions of the cerebellum.
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Disclosures: C. Wang: None. **Y. Wang:** None. **X. Yuan:** None.

Poster

652. Autism: Synapses and Circuits

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Program#/Poster#: 652.07/C1

Topic: A.07. Developmental Disorders

Support: NIH Grant R01 MH107223

DOD/CDMRP 13-1-0440

Title: Altered HDAC4 localization in a mouse model of maternal immune activation

Authors: P. COIRO, L. BERGDOLT, Y. JUNG, *A. DUNAEVSKY
Developmental Neurosci., Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Infections during pregnancy are associated with increased risk of psychiatric disorders in offspring, including autism spectrum disorder and schizophrenia. The viral mimic Poly(I:C) is often used in rodent models of maternal immune activation (MIA). We and others have previously shown altered cytokine expression and synapse number in brains of mouse MIA offspring that were associated with altered behaviors. Here we investigated the molecular mechanisms that might mediate the reduced number of synapses observed in MIA offspring. Specifically, we have tested the hypothesis that MIA induces epigenetic changes in the fetal brain which involve the nuclear translocation of the histone deacetylase HDAC4, resulting in a long-lasting impact on synaptic structures. We report that in neurons of MIA offspring, both in culture and in vivo, there is nuclear accumulation of HDAC4, which belongs to class IIa HDACs and is mainly cytoplasmic in basal conditions. This altered subcellular localization is associated

with a reduction of phospho-HDAC4 that is necessary for the nuclear export. In MIA offspring we also find activation of extracellular signal-regulated kinase ERK1/2 that has been shown to be activated by cytokines and lead to nuclear translocation of HDAC4. Nuclear accumulation of HDAC4 was correlated with a reduction in number of spines. Moreover, HDAC4 makes a complex with another class I HDAC, HDAC3, resulting in a total reduction of the acetylation of Histone H3. Finally, using a specific inhibitor for HDAC4, we were able ameliorate the reduction in number of spines in cultured neurons from MIA offspring. Current efforts are underway to determine if postnatal administration of HDAC4 inhibitor can ameliorate the behavioral impairments associated with MIA.

Disclosures: **P. Coiro:** None. **L. Bergdolt:** None. **Y. Jung:** None. **A. Dunaevsky:** None.

Poster

652. Autism: Synapses and Circuits

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Topic: A.07. Developmental Disorders

Support: NIH Grants MH103021, HD042182

Simons Foundation Research Grant (SFARI306796)

Title: Cortico-cortical underconnectivity in the lgdel mouse model of digeorge/22q11.2 deletion syndrome

Authors: *D. W. MEECHAN[1,3], A. FERNANDEZ[3], B. KARPINSKI[3], E. PARONETT[3], H. RUTZ[2], C. BRYAN[3], E. RADIN[3], N. BARON[4], D. CONTRERAS[4], L. ROTHBLAT[5], T. MAYNARD[3], A.-S. LAMANTIA[3]
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Abstract: We show for the first time that diminished dosage of genes deleted in 22q11 Deletion Syndrome (22q11DS), which is associated with autistic spectrum disorders (ASD) and schizophrenia (Scz), results in cortico-cortical under-connectivity. Mapping of cortical projections in the *LgDel* 22q11DS mouse model reveals under-connectivity between the medial frontal cortex and other cortical association areas.
These changes are reflected in eletrophysiological responses measured in the *LgDel* medial frontal cortex following stimulation from other cortical areas. Furthermore, the dendritic and

axonal growth of the layer 2/3 projection neurons (PNs) that make the majority of cortico-cortical connections are dysmorphic. *In vivo* and *in vitro*, dendritic length and complexity as well as axon length is reduced in *LgDel* Layer 2/3 projection neurons (PNs). Using scanning electron microscopy with back-scatter detection to resolve individual synapses, we found a significantly diminished frequency of synaptic contacts on the dendrites of identified layer 2/3 PNs. The synaptic contacts that remain on LgDel layer 2/3 PN primary dendrites and in the adjacent layer 2/3 neuropil have reduced numbers of synaptic vesicles in presynaptic processes as well as decreased thickness and size of post-synaptic densities. We also observed hallmarks of cellular stress in these neurons that include distended mitochondrial cristae-indicative of altered reactive oxygen species (ROS) levels. Disrupted function of a 22q11 mitochondrial gene, *Txnrd2*, recapitulates these phenotypes. *Txnrd2* over-expression in *LgDel* restores WT ROS levels as well as synapse, dendrite and axon growth *in vitro*. Targeted, sparse recombination of one mutant allele of *Txnrd2* (*Txnrd2*$^{+/fl}$) using a Cux2:CRE^{ERT} driver in layer 2/3 PNs *in vivo* recapitulates, at comparable magnitudes, the dendritic growth deficits seen in the *LgDel*. The antioxidant, N-acetyl cysteine (NAC), also reverses these changes in *LgDel*, *Txnrd2*-depleted and *Txnrd2*$^{+/-}$ layer 2/3 PNs in vivo. Finally, preliminary work suggests that some behavioral deficits seen in LgDel mice may be partially or completed reversed by NAC treatment from birth onward. Thus, *Txnrd2*-dependent redox regulation underlies cortico-cortical under-connectivity in a genetically valid mouse model of 22q11DS. Our data establishes under-connectivity as a consequence of a genomic lesion associated with ASD and Scz, and related cortical circuit disorders and suggests a new, safe therapeutic approach for ameliorating cortical circuit pathogenesis and behavioral deficits in neurodevelopmental disorders.

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Poster

652. Autism: Synapses and Circuits

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.09/C3

Topic: A.07. Developmental Disorders

Support: R21HD084953

Title: Distinct changes in striatal glutamate efflux during grooming behavior in the BTBR mouse model of autism

Authors: *J. T. DUNN, R. OCAMPO, M. E. RAGOZZINO
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Abstract: Restricted interests and repetitive behaviors (RRBs) comprise a core symptom domain of autism spectrum disorder (ASD). Such behaviors exist in both cognitive forms (e.g. insistence on sameness) as well as compulsive-like motor behaviors (e.g. repetitive hand movements, body rocking). One prevalent hypothesis related to the neuropathophysiology underlying the ASD behavioral phenotype suggests that an imbalance of excitation and inhibition exists within a cortico-basal ganglia-thalamo-cortical circuit. More specifically, dysfunction of this circuit may stem from altered cortico-striatal glutamatergic transmission. Mouse models of ASD such as the BTBR T+Itpr3tf/J (BTBR) mouse model of idiopathic autism offer an opportunity to explore this hypothesis, as they have previously been shown to engage in repetitive self-grooming behavior representative of compulsive-like RRBs observed in ASD. Through the use of glutamate biosensors (Pinnacle Technology Inc., Lawrence, KS), we were able to assess real-time changes in glutamate concentration within the dorsomedial striatum while BTBR mice and C57BL6/J (B6) control mice engaged in self-grooming behavior. Grooming behavior was measured across a 10 minute testing period in a clear, plastic container. The testing period was video recorded by a camera synced to the glutamate signal produced by the implanted biosensor. As previously reported, BTBR mice demonstrated elevated self-grooming behavior compared to B6 controls. Interestingly, preliminary data indicate that while a decrease in glutamate concentration was observed during bouts of grooming in B6 control mice, an increase in BTBR dorsomedial striatum glutamate concentration was observed during self-grooming behavior. These preliminary findings suggest that both the direction and magnitude of changes in glutamate concentration within the striatum may be key in understanding the driving factors of RRBs in ASD.

Disclosures: J.T. Dunn: None. **R. Ocampo:** None. **M.E. Ragozzino:** None.

Poster

652. Autism: Synapses and Circuits

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Program#/Poster#: 652.10/C4

Topic: A.07. Developmental Disorders

Support: NIMH Grant R00MH099243

Title: Altered nucleus accumbens activity as a shared neural circuit defect for autism-related behaviors

Authors: *M. F. DAVATOLHAGH[1], K. CHOI[1], J. LYNCH[2], T. O'BRIEN[1], T. ABEL[2], M. V. FUCCILLO[1]
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Abstract: Autism spectrum disorders (ASD) are neurodevelopmental abnormalities characterized by impairments in two core domains: social interaction/communication and repetitive, stereotyped behaviors. While candidate gene approaches have revealed a growing number of genes implicated in ASD, it has been difficult to investigate pathophysiological mechanisms due to the polygenic nature of the disease. One potential approach is to identify specific neural circuits that mediate ASD-associated behaviors. Studies have implicated the nucleus accumbens as a brain region whose dysfunction has been attributed to deficits in both social reward and motor control. We hypothesize impaired synaptic transmission in the nucleus accumbens as a recurring neural circuit defect that mediates motor abnormalities associated with ASD. To examine ASD-related motor behaviors we used the accelerating rotating rod (rotarod) as a measurement of the formation of repetitive motor routines, correlating learning rate and stereotyped motor output. As the enhanced rotarod phenotype has been demonstrated across multiple mouse models, we will employ this task as a behavioral "endophenotype" in our attempt to uncover a common neural circuit abnormality in genetic models for ASD. We have confirmed that both Neurexin-1α and 16p11.2$^{del/+}$ ASD-associated genetic models have increased learning rate on the rotarod. To examine global synaptic changes onto neurons in the nucleus accumbens, whole-cell voltage-clamp recordings were performed. Preliminary results suggest that both Neurexin-1α and 16p11.2$^{del/+}$ animals have significant alterations in synaptic transmission within the nucleus accumbens. Together, these findings provide further evidence for altered activity in the nucleus accumbens in autism etiology. Future experiments will explore accumbal physiological alterations *in vivo* during rotarod learning in an attempt to understand whether mutation-associated synaptic changes are driving repetitive motor output in these two genetic models.

Disclosures: M.F. Davatolhagh: None. **K. Choi:** None. **J. Lynch:** None. **T. O'Brien:** None. **T. Abel:** None. **M.V. Fuccillo:** None.

Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.11/C5

Topic: A.07. Developmental Disorders

Title: Autism Spectrum Disorders may be caused by developmental dysregulation of polyamine metabolism

Authors: *A. J. SOKOLOFF
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Abstract: Heritability of Autism Spectrum Disorders (ASD) is likely overstated because of the uncertain genetic significance of monozygotic twin (MZ) studies due to monochorionic

placentation in most MZ pregnancies. To identify non-genetic biological processes that can cause ASD, studies were searched in Pubmed by key words “maternal autism risk factors” (M-ASD-RF), “gestational autism risk factors” (G-ASD-RF), “autism neural phenotype” (ASD-NP), “autism neuroanatomy” and by manual search of developmental literature to identify metabolic pathways linking RF and NP. Despite differences by study, likely M-RF for increased ASD were autoimmune disease, diabetes (M,G), infection, intestinal disorders, obesity, elevated sex steroids, short and long inter-birth interval, thyroid peroxidase auto-antibody and vitamin D deficiency. Likely G-RF for increased ASD were hypoxia, ischemia, pre-eclampsia, preterm birth and preterm small for gestational age, term large for gestational age, and exposure to valproic acid and some environmental toxins. Equivocal RFs, e.g., SSRI, smoking, were not considered. NPs with the most common penetrance were evaluated (cerebellar hypo/hyperplasia, Purkinje dysgenesis; cerebral overgrowth, variation in neuronal migration and connectivity, cortical dysgenesis; amyloidosis). A review of >5,000 peer-reviewed studies in human and non-human in vivo and in vitro systems revealed that a single pathway, polyamine metabolism (PA), connected increased ASD-RF to ASD-NP. The conclusion that developmental PA dysregulation (PA-DYS) causes ASD was supported by robust PA in factors with decreased ASD risk (thyrotoxosis, preconceptual/early-G folic acid). I conclude that developmental PA-DYS causes ASD. PA is essential for fundamental cellular (e.g., transcription, translation, cell-cycle) and neurodevelopmental (e.g., neurogenesis, differentiation, migration; axogenesis; synaptogenesis) processes; thus neural consequences of PA-DYS can be variable by timing, localization, mode (e.g., synthesis, catabolism) and molecular interactions of PA-DYS. Such variability in PA-DYS may explain differences in ASD-NP and may underlie temporal windows of certain RFs. Because PA is essential for placenta vascular, immune and hormonal function, placenta modification by PA-DYS can substantially impact ASD-NP. Requirement of PA in DNA repair suggests that many de novo mutations in ASD are correlative of PA-DYS and not causal of ASD. These findings suggest that PA biomarkers may enable identification of some at-risk pregnancies and infants, and restoration of PA homeostasis may mitigate some fraction of ASD risk.

Disclosures: A.J. Sokoloff: None.

Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.12/C6

Topic: A.07. Developmental Disorders

Support: CONACYT Scholarship No. 230354

Title: Density of cannabinoid receptors of autistic rat after musical stimulation

Authors: *D. MONJE[1], J. MANZO[2]
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Abstract: Endocannabinoids are involved in several processes related to activities such as learning and memory. In autism, it has been seen that the alteration in cannabinoids has an impact on the manifestation of symptoms such as response to social reward and anxiety. But there are no pharmacological treatments to reverse these effects. Therefore, defining strategies to recover the changes in the cannabinoids of the autistic brain is fundamental. This work started from this premise. Musical stimulation in various animal models has shown positive effects on neurorehabilitation. In autism, these effects are beginning to appear. We have been working on the role of the cerebellum in the learning and motor control of Wistar rats, and documented the fluctuation of cannabinoid receptors in subjects with normal development. In this study we analyzed the modification of these receptors in an autism model, to determine the effect of musical stimulation on their density in the cerebellum. We worked with a postnatal model of autism, which is produced by injecting a dose of 400 mg / kg of valproic acid at PN10 day. From day PN1 to PN30, subjects received musical stimulation daily for one hour, with Mozart sonatas, at an intensity of 70dB. Then, the cerebellar fluoculous were obtained to be analyzed by immunohistochemistry for CB1 receptors. The results showed that the density of CB1 receptors does not change significantly in the autistic subjects, but the subjects with musical stimulation present a smaller variability between them. This information reveals that the system of cannabinoids in the cerebellum of control and autistic subjects is similar and respond in the same way to musical stimulation. CONACYT Scholarship No. 230354 (DMR), Cuerpo Academico de Neurociencias (UV-CA-28) and Neuroquímica (UV-CA-304).
Keywords: autism, cannabinoids, music.

Disclosures: **D. Monje:** None. **J. Manzo:** None.

Poster

652. Autism: Synapses and Circuits

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Program#/Poster#: 652.13/C7

Topic: A.07. Developmental Disorders

Support: NIH R00HD067379

Pilot Project grants from the Intellectual and Developmental Disabilities Research Center (IDDRC) at Children's National

Title: The Intelectual disability gene CC2D1A regulates subcellular localization of AKT signaling in neurons

Authors: *P. A. MUÑOZ LLANCAO, A. W. OAKS, E. J. FARROW, M. C. MANZINI
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Abstract: Intellectual Disability (ID) and Autism Spectrum Disorder (ASD) are common neurodevelopmental disorders, in which many signaling molecules are mutated or dysfunctional, stressing a critical role for intracellular signaling in cognitive development. In this context, mutations in the CC2D1A (coil-coiled and C2-domain containing 1A) gene has been shown that cause a spectrum of phenotypes including non-syndromic ID, ASD and seizures. CC2D1A has the structure of a scaffold characterized by four DM14 domains, protein-binding domains unique to this protein and its homolog CC2D1B. Through these domains, CC2D1A interacts with a variety of signaling proteins (e.g AKT, PKA, and NF-κB pathway) involved in transcription, endosomal signaling, and membrane trafficking modulation.
Our hypothesis is that CC2D1A controls AKT signaling by targeting it to specific subcellular regions promoting localization of signaling events. We find that AKT signaling is altered in both non-neuronal cell lines (HEK293) and primary neurons when CC2D1A is overexpressed or removed. Using immunocytochemistry, we detected active/phosphorylated Akt (pT308) in conjunction with recycling endosomes following CC2D1A overexpression in HEK293 cells. To determine whether overexpression of CC2D1A changes the subcellular distribution of active AKT, we used Förster resonance energy transfer (FRET) biosensor for AKT activity, Eevee-iAkt. We then performed fluorescence lifetime imaging (FLIM) in HEK293 cells to validate the FRET signal. We found that overexpression of CC2D1A lead an increased in FRET emission at the plasma membrane of the cells and at the endolysosomal machinery.
One important function of AKT in neurons is downstream of brain derived neurotrophic factor (BDNF), which is critical for neuronal differentiation, function and plasticity. Analysis in cortical neurons generated from Cc2d1a knock-out embryos showed an enhancement in AKT activation following BDNF treatment. In parallel, AKT phosphorylation is increased in lysates from the brain of adult Cc2d1a-deficient animals. We are now evaluating AKT activity by FRET in primary neurons from wild type and Cc2d1a KO mice following BDNF treatment, to analyze where activated AKT is localized in the cell body and dendritic arbor.
Taken together our result show that CC2D1A regulates the subcellular localization of AKT signaling at the plasma membrane and endolysosomal vesicles. This function may regulate intracellular signaling response downstream of BDNF controlling neuronal differentiation and leading to intellectual disability when disrupted.

Disclosures: P.A. Muñoz Llancao: None. **A.W. Oaks:** None. **E.J. Farrow:** None. **M.C. Manzini:** None.

Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.14/C8

Topic: A.07. Developmental Disorders

Title: Negr1 together with FGFR2 and PCDH19 regulate cortical development and core behaviors related to autism spectrum disorders in rodents

Authors: *L. CANCEDDA[1,2], B. PINTO[1,3], J. SZCZURKOWSKA[1], A. CWETSCH[1], F. PISCHEDDA[4], L. PERLINI[1], S. BASSANI[5], F. MANAGO[1], C. HAAS[6], R. BERTORELLI[1], M. SUMMA[1], F. PAPALEO[1], M. SCHAFER[6], M. PASSAFARO[5], G. PICCOLI[4,2]
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Abstract: Disruption in neural migration and/or defective morphological maturation can lead to brain malformations with functional consequences on proper wiring of the neuronal network, as already described in neurodevelopmental disorders such as Autism Spectrum Disorders (ASD). Common knowledge indicates cell-adhesion molecules (CAMs) and Receptor tyrosine kinases (RTKs) as essential for proper neural migration and spine maturation. Moreover, ERK and AKT are convergent signaling pathways downstream to many RTKs and highly implicated in autism. Here, we identified three proteins (previously associated to ASD), which possibly form a multiprotein complex that regulates ERK and AKT signaling, cortical development and core behaviors related to autism. In particular, by *in utero* electroporation coupled with RNA interference (siRNA), we downregulated alternatively the expression of CAMs Neuronal Growth Regulator 1 (Negr1) and Protocadherin 19 (PCDH19), as well as the RTK Fibroblast Growth-Factor Receptor 2 (FGFR2) in late-born pyramidal neurons migrating to the superficial layers of the neocortex. We found that all three siRNA manipulations caused ectopic positioning of neurons concentrated at the border between layer 5 and layer 4 in the somatosensory cortex and reduced spine density. In agreement with association of Negr1, FGFR2, and PCDH19 to autism, we found that their downregulation in the somatosensory cortex resulted in a decreased number of ultrasonic vocalizations in pups, increased pain threshold and decreased social interactions in juvenile animals. Interestingly, we found that Negr1, FGFR2 and PCDH19 physically interact with one another and that Negr1 modulates FGFR2-ERK and AKT signaling by decreasing FGFR2 degradation from the plasma membrane *in vitro*. Accordingly, FGFR2 overexpression rescues all anatomical and behavioral defects observed upon Negr1 knock-down. Finally, the above findings were confirmed by the defective cortical layering and behavior in Negr1 knock out mice. These data suggest that the Negr1/FGFR2/PCDH19 complex, is necessary for proper

cortical development, as well as for core behaviors related to ASD by possibly activating ERK/AKT.

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Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.15/C9

Topic: A.07. Developmental Disorders

Title: A sex difference in oxytocin-expressing cells and serotonin receptors in the paraventricular nucleus after developmental serotonin exposure

Authors: *K. WAGNER, S. L. ZUP
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Abstract: The developmental hyperserotonemia (DHS) model of Autism Spectrum Disorder (ASD) utilizes perinatal administration of serotonin (5HT) agonist 5-methoxytptamine (5-MT) to mimic the elevated blood 5HT levels observed in many ASD individuals. DHS produces behavioral and brain morphological changes relevant to ASD, such as dysregulation of oxytocin (OXT)- a hormone implicated in social behavior regulation. 5HT can influence OXT release via its receptors 5-HT_{1A} and 5-$HT_{2A,}$ which co-localize in OXT+ cells in the paraventricular nucleus (PVN) of the hypothalamus. Thus, DHS may induce abnormal social behavior by acting during development to decrease the number of OXT+ cells and/or the likelihood of OXT+ cells to release OXT into circulation. The most parsimonious mechanism of 5HT action would be via alteration of 5HT receptors on OXT+ cells. In addition, there are pronounced sex differences in both developmental 5HT regulation and ASD diagnosis, suggesting that 5HT may alter OXT differently between males and females. Despite this, most DHS studies are only performed in males. We directly compared the number of OXT+ cells and percentage of OXT+ cells expressing $5HT_{1A}$ and $5HT_{2A}$ receptors between adult male and female DHS rats. We report sex differences in the number of OXT+ cells as well as their expression of 5HT receptors in the PVN. In agreement with previous findings, adult DHS males had fewer OXT+ cells than controls. Adult DHS females, however, had the same number of OXT+ cells as controls. Both DHS males and females had a lower percentage of OXT+ cells expressing excitatory $5HT_{2A}$ receptors than controls, but only DHS females had a higher percentage of OXT+ cells expressing inhibitory $5HT_{1A}$ receptors. This expression pattern suggests that females, but not males, can regulate 5HT receptors after DHS in a manner that promotes OXT+ survival and functional

efficiency. These data are especially interesting in light of previous findings that juvenile DHS males, but not females, have a 5HT receptor profile that favors excitability in the PVN. We hypothesize that DHS leaves OXT+ cells in males vulnerable to over-excitation and cell death, whereas females can compensate to thus produce the appropriate number of OXT+ cells by adulthood.

Disclosures: K. Wagner: None. **S.L. Zup:** None.

Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.16/C10

Topic: A.07. Developmental Disorders

Support: NIH R21 MH108909

Title: Differential alternative splicing in superior temporal gyrus of autism spectrum disorder brains

Authors: B. STAMOVA[1], B. P. ANDER[2], A. OMANSKA[3], M. DUROCHER[2], F. SHARP[2], *C. M. SCHUMANN[3]
[1]Neurol., Univ. of California, Davis Sch. of Med., Sacramento, CA; [2]Neurol., [3]Psychiatry and Behavioral Sci., UC Davis MIND Inst., Sacramento, CA

Abstract: Objectives: Gene expression studies in postmortem brain in Autism Spectrum Disorders (ASD) have revealed dysregulated immune and neuronal networks, and implicated differential alternative splicing (DAS). Thus, we investigated DAS and the co-expression structure in the superior temporal gyrus (STG) of brains of ASD subjects compared to typically developing controls (TD). STG is an association cortex involved in social, speech, and face perception, joint attention, and implicated in ASD. **Methods:** RNA libraries from 45 subjects (16 ASD, 14/2 M/F; 29 TD, 23/6 M/F) were sequenced to 40M 2×150 bp reads. DAS was assessed using Log-normal with shrinkage models and a Gene-Specific algorithm, considering Diagnosis, Sex and Age. DAS was considered significant with |Fold-Change| >1.2, and FDR-corrected $p<0.3$ (nominal $p<0.01$). Weighted Gene Co-expression Network Analysis (WGCNA) was performed on gene-level expression to define modules of co-expressed genes in TD and ASD (unsigned networks; preservation Z-statistics). **Results:** 330 genes showed DAS in ASD vs. TD considering both sexes: 795 in ASD-Male vs. TD-Male, and 41 in ASD-Female vs. TD-Female. Genes with DAS were over-represented in immune and neurotransmitter pathways, some of which have previously been implicated in ASD. There was no significant age difference between ASD (Average age: 30 years, range 9-56)) and TD (Average age: 25.2, range 5-68) groups. There was significant overlap with ASD-implicated genes with all ASD vs. TD (33 genes,

p=1.3E-06) and ASD-Male vs TD-Male (81 genes, p=7.9E-15) DAS gene lists. Among them, the RBFOX2-12 transcript was down-regulated in ASD-Male. RBFOX2 (RNA Binding Protein, FOX1 Homologue 2) regulates alternative splicing in the nervous system and is homologous to FOX1 (A2BP1), a neural-specific splicing regulator reported to be down-regulated in ASD brain (Voineagu et al, 2011). There was a significant overlap with our all ASD vs. TD (9 genes, p=0.004) and ASD-Male vs. TD-Male (32 genes, p=4.1E-12) gene lists when compared to the 196 genes with FOX1-dependent DAS identified by Voineagu et al. WGCNA revealed perturbation in co-expression in several modules and a number of ASD-implicated genes were hub genes in modules with low preservation, potentially affecting nervous system development and function (MECP2, PTEN, MAPK1, DYRK1A, DOCK4, GNAS), such as potentiation of synapse, quantity of neurons, dendritic branching and prepulse inhibition. **Conclusions:** There is differential alternative splicing in the STG region of ASD brains which is modulated by age and sex. WGCNA also revealed hub genes which have been implicated in ASD.

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Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.17/C11

Topic: A.07. Developmental Disorders

Support: SFARI 342096, “Comparison of cortical circuit dysfunction in ASD model mice”

Title: Altered excitatory-inhibitory ratio preserves circuit excitability in FMR1, CNTNAP2, 16p11.2 deletion, and Tsc2 mouse models of autism

Authors: *T. LANGBERG[1], M. W. ANTOINE[2], P. SCHNEPEL[3], D. E. FELDMAN[4]
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Abstract: Distinct genetic forms of autism are widely hypothesized to share a common circuit basis in increased excitation-inhibition (E-I) ratio in cerebral cortex, causing hyperexcitability and excess spiking. We tested this hypothesis by comparing synapse and circuit physiology in L2/3 of somatosensory cortex in four transgenic mouse models of autism ($CNTNAP2^{-/-}$, $FMR1^{-/y}$, 16p11.2 deletion, $Tsc2^{+/-}$). All strains showed reduced L4-evoked IPSCs in L2/3 pyramidal cells coupled with a more moderate and variable reduction of EPSCs, thus increasing E-I ratio versus wild types. mIPSCs and mEPSCs showed only modest or inconsistent changes in autism

genotypes. Remarkably, reductions in evoked IPSCs and EPSCs were quantitatively matched to drive stable—not increased—peak synaptic potentials relative to wild type. This suggests that the L2/3 network may have normal, not enhanced, excitability. Consistent with this prediction, spontaneous network-driven spiking in L2/3 of active slices was normal in autism models, except for elevation in CNTNAP2$^{-/-}$ mice. To test whether these synaptic changes alter circuit excitability in vivo, we recorded whisker-evoked spiking in L2/3 of the CNTNAP2, FMR1, and 16p11.2 strains under urethane-anesthesia. Regular-spiking (RS, presumed excitatory) units showed increased spontaneous firing only in CNTNAP2$^{-/-}$ mice. Whisker-evoked RS unit firing was normal in CNTNAP2$^{-/-}$ and 16p11.2 deletion mice, and was reduced in FMR1$^{-/y}$ mice. Sensory tuning was unchanged in all genotypes, except for reduced tuning preference for the columnar whisker in FMR1$^{-/y}$ mice. Thus, excitability and sensory processing in L2/3 of autism strains was remarkably normal, despite the substantial reduction in L4-L2/3 inhibition. We hypothesize that inhibitory weakening in autism mutations contributes to homeostatic stabilization of net synaptic drive, rather than driving circuit hyperexcitability, at least for low-frequency stimuli.

Disclosures: **T. Langberg:** None. **M.W. Antoine:** None. **P. Schnepel:** None. **D.E. Feldman:** None.

Poster

652. Autism: Synapses and Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 652.18/C12

Topic: A.07. Developmental Disorders

Support: R01MH110487

PHRF

Title: Decreased spontaneous network activity in a mouse model of Pitt-Hopkins Syndrome, a rare form of autism spectrum disorder (ASD)

Authors: *H.-Y. CHEN, G. R. HAMERSKY, S. C. PAGE, B. J. MAHER
Developmental Electrophysiology, Lieber Inst. For Brain Develop., Baltimore, MD

Abstract: Pitt-Hopkins Syndrome (PTHS) is a rare form of autism spectrum disorder (ASD) that is caused by de novo mutation in one copy of the transcription factor 4 (TCF4) gene. This gene belongs to type 1 basic helix-loop-helix (bHLH) transcriptional factor family and is able to form homodimer or heterodimer with other members in this gene family for gene regulation in a tissue specific manner. Using a mouse model of PTHS that produces a truncated TCF4 protein (TCF4+/tr), we previously reported that medial prefrontal pyramidal neurons display intrinsic

excitability deficit that are partially due to ectopic upregulation of SCN10a (Rannals et al., Neuron 2016). Here, we ask whether these cellular level excitability deficits have any impacts on synaptic transmission and network activity. We studied spontaneous neurotransmission with whole-cell patch clamp and network activity using Ca2+ imaging in acute prefrontal brain slices. We observed that TCF4+/tr neurons showed decreased frequency and amplitude of spontaneous excitatory synaptic currents (sEPSCs) onto pyramidal neurons. However, this effect was abolished in the presence of TTX suggesting that it was dependent on the generation of spontaneous action potentials. We also observed a significant reduction in the frequency of spontaneous inhibitory currents (sIPSCs) onto these pyramidal neurons. Similarly, this effect was sensitive to application of TTX, suggesting a dependence on the generation of spontaneous action potentials. To test for a generalized deficit in spontaneous action potentials in the prefrontal cortex of this PTHS mouse model Ca2+ imaging experiments are ongoing. These results herein together with intrinsic excitability deficit suggests pyramidal cells in this PTHS mouse model have an overall decrease in their ability to generate spontaneous action potentials and this leads to a generalized decrease in network activity. We hypothesize these excitability deficits in prefrontal cortical networks represent pathophysiology in PTHS that may underlie cognitive deficits observed in this patient population.

Disclosures: **H. Chen:** None. **G.R. Hamersky:** None. **S.C. Page:** None. **B.J. Maher:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 653.01/C13

Topic: A.07. Developmental Disorders

Title: Understanding interneurogenesis in a novel model of neonatal brain injury

Authors: *H. LACAILLE[1], C. M. VACHER[1], A. PENN[1,2]
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Abstract: Preterm birth is a leading cause of neonatal encephalopathy that can lead to long-term neurological impairment. Maternal immune activation (MIA), seen in 85% of extremely preterm births, and extreme prematurity itself has been implicated in the resulting neurodevelopmental disorders. A common feature of these disorders is an imbalance between neuronal excitation and inhibition, mediated by developmental alterations of GABAergic interneurons, especially in the prefrontal cortex (PFC). Interneurons are generated through late gestation and mature after birth; increasing evidence suggests that abnormal interneuron development after preterm birth is a critical mechanism underlying cortical dysfunction. To test our hypothesis that alterations in GABAergic interneurons play a key role in preterm encephalopathy and its long-term functional

consequences, we developed a novel pre-clinical model combining mild pre- and postnatal insults: LPS exposure in late rodent gestation (MIA, modeling prenatal infection/inflammation) followed by postnatal chronic sublethal hypoxia (CSH, modeling poor lung function of preterm birth). Using GAD65-GFP transgenic mice to mark GABAergic interneurons, PFC development was assessed. Independently, MIA or CSH lead to transient or limited interneuron disruption. We previously reported that prenatal LPS exposure alone altered progenitor proliferation in the ganglionic eminence, plus migration and survival of these cells at embryonic day E17.5; however, significant rebound recovery appeared to occur. In contrast, sequential use disrupted multiple maturational steps, permanently altering cortical GABAergic circuits, while leaving the majority of NeuN+ excitatory neurons intact. At postnatal day 30 (P30), there was significant loss of GFP+ cells, reflecting loss of multiple interneuron subtypes (parvalbumin, somatostatin, NPY, calbindin, calretinin) in the PFC. Further investigations are focused on deciphering the mechanisms of interneuron loss and the potential for recovery at later developmental stages. Understanding alteration of interneuron populations after neonatal injuries is a critical step in developing targeted therapies to prevent the cortical dysfunction associated with extremely preterm birth.

Disclosures: H. Lacaille: None. **C.M. Vacher:** None. **A. Penn:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 653.02/C14

Topic: A.07. Developmental Disorders

Support: Mayo Clinic Children's Research Center Pediatric Team Science Award

Title: Differences in lumbar motor neuron pruning in an animal model of early onset spasticity

Authors: *J. E. BRANDENBURG[1,2], H. M. GRANSEE[3], W. Z. ZHAN[4], M. J. FOGARTY[4], G. C. SIECK[4,3]
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Abstract: Spastic Cerebral Palsy (sCP) is the most common motor disability of childhood with spasticity being the most common sign and ambulation always affected. Despite sCP being poorly predicted by brain imaging, the focus of research has remained on the brain being the driver of the motor impairment and spasticity. By contrast, motor neurons (MNs), via the motor unit and neurotransmitter signaling, are the ultimate target of most clinical therapeutic spasticity treatments in sCP, are the final common output of motor control, and are poorly understood in sCP. MN development in sCP is a critical knowledge gap as the late embryonic and postnatal

periods are not only when the supposed brain injury occurs in sCP, but is a critical time for spinal cord neuromotor development. Therefore, using an animal model of early onset spasticity (*Spa* mouse [B6.Cg-*Glrb*^{spa}/J] with a Gly receptor mutation), we have focused our work on evaluating lumbar MN and motor unit physiology. Similar to previous work in other glycine mutants, we hypothesized that *Spa* mice will have decreased lumbar MN pruning (i.e. a greater number of MNs) with MNs having a smaller somal size. 5-9 week-old *Spa* (Glrb$^{-/-}$) and wildtype (Glrb$^{+/+}$) mice from our *Spa* mouse colony underwent unilateral retrograde labeling of the tibialis anterior (TA) muscle MNs (L2-L4 innervation) via nerve dip of the peroneal nerve. Three days following nerve dip, mice were euthanized, perfused with 4% paraformaldehyde and lumbar spinal cord excised and processed for longitudinal cryosectioning (70-100 µm) and prepared for confocal imaging. Absolute lumbar TA MN counts were obtained using mosaic images of adjacent serial sections, with *Spa* mice having 60% fewer MNs compared to wildtype mice (P<0.01). Somal size measurements were obtained using ImageJ with *Spa* mice having a ~34% reduction compared to wildtype mice (P<0.01). MN pruning and somal size is clearly abnormal in early onset spasticity and is contrary to our hypothesis. Our work now has a two-fold focus. One, as previous work has been in fetal mice; we are exploring MN pruning and somal size in fetal *Spa* and perinatal mice to further understand the timing of the MN pruning. Two, we also propose that these gross alterations in MN pruning may underpin the impaired neuro-motor transmission and force generation in this model of sCP, which are a focus of other ongoing studies.

Disclosures: J.E. Brandenburg: None. **H.M. Gransee:** None. **W.Z. Zhan:** None. **M.J. Fogarty:** None. **G.C. Sieck:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 653.03/C15

Topic: A.07. Developmental Disorders

Support: MRC CNGG

Title: Investigating the neural mechanisms that underlie neurodevelopmental disorders associated with EHMT1

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Abstract: *Euchromatic Histone Methyltransferase 1 (EHMT1)* encodes a histone methyltransferase of critical importance for heterochromatin formation and gene silencing.

Haploinsufficiency of *EHMT1* is the primary cause of Kleefstra Syndrome. Additionally, CNVs spanning *EHMT1* have also been associated with Autism spectrum disorder (ASD) and schizophrenia. Further genetic studies have also linked *de novo* mutations affecting *EHMT1* to developmental delay more generally. The severity and breadth of neurodevelopmental phenotypes associated with changes in *EHMT1* dosage are a strong indication of the central importance of this gene. However, a clear understanding of its role in the development and function of the brain is still lacking. Work in our lab showed that *Ehmt1*$^{+/-}$ mouse embryonic stem cells (ESCs) could be differentiated into biochemically normal neural progenitor cells but in significantly reduced numbers, suggesting a neurogenic component to *EHMT1*. Here we aim to explore the role of *Ehmt1* in the brain further, using both a cellular and animal model approach. We have established a novel conditional heterozygous knockout *Ehmt1* mouse line by crossing a floxed *Ehmt1* mouse line with a D6-Cre mouse line leading to forebrain specific deletion mouse model (*Ehmt1*$^{D6cre/+}$). To discern whether haploinsufficiency of *Ehmt1* leads to altered neurogenesis using BrdU on sectioned brain samples from adult *Ehmt1*$^{D6cre/+}$ knockouts and *Ehmt1*$^{flx/+}$ littermate controls. Initial data suggests a trend towards an increase in proliferation in the adult *Ehmt1*$^{D6cre/+}$ compared to the *Ehmt1*$^{flx/+}$ littermate controls. We are now going on to assess survival and differentiation rates differences in these mice. Additionally, these *ex vivo* data was complemented by analysis of primary cell cultures derived from *Ehmt1*$^{D6cre/+}$ brain. Analyses of the neuronal phenotypes found that *Ehmt1*$^{D6cre/+}$ cells showed impaired maturation compared to WT controls, with a significant reduction in DCX+ cells. To complement these findings, RNA-Seq analysis on the primary cell cultures will be undertaken. Finally, the functional consequence of *Ehmt1* haploinsufficiency in the brain has been assessed using behavioural tasks of relevance to the associated neurodevelopmental disorders and/or linked to neurogenesis. We demonstrate that *Ehmt1*$^{D6cre/+}$ knockouts have deficits in sensorimotor gating using the acoustic startle task, and impaired learning and memory using the novel object recognition task and 1-choice serial reaction time task. Taken together, these data provide insight into the neural mechanism that underlie the neurodevelopmental disorders associated with *EHMT1* mutation.

Disclosures: **M. Adam:** None. **N. Haan:** None. **T. Humby:** None. **A.R. Isles:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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NIH, NINDS, K08-NS099502 (MR)

Howard Hughes Medical Institute (EE)

Title: Genetic mapping of developing brainstem motor neuron subtypes: Implications for their differential susceptibility to disease

Authors: *M. F. ROSE[1], *M. F. ROSE[1,3,2,4,5], M. A. TISCHFIELD[2], A. GELBER[2], A. A. NUGENT[2,6], P. ANG[2], S. IZEN[2], W. HUANG[2,7], R. SATIJA[8,9], O. ROZENBLATT-ROSEN[5], A. REGEV[5,10], E. ENGLE[2,4,5,10]
[1]Pathology, [2]Neurol. and F.M. Kirby Neurobio. Ctr., Boston Children's Hosp., Boston, MA; [3]Pathology, Brigham and Women's Hosp., Boston, MA; [4]Harvard Med. Sch., Boston, MA; [5]Broad Inst. of MIT and Harvard, Cambridge, MA; [6]Grad. Sch. of Arts and Sci., Harvard Univ., Boston, MA; [7]Sch. of Med., Zhejiang Univ., Hangzhou, China; [8]New York Genome Ctr., New York City, NY; [9]Biol., New York Univ., New York City, NY; [10]Howard Hughes Med. Inst., Boston, MA

Abstract: Eye movements are controlled by distinct motor nuclei in the brainstem that have differential vulnerability to disease. In some congenital cranial dysinnervation disorders (CCDDs), specific subsets of ocular motor neurons (OMNs) show dysinnervation, while other motor neuron (MN) subtypes are unaffected. In contrast, OMNs continue to function until late in the course of Amyotrophic Lateral Sclerosis (ALS), while spinal and other brainstem MNs degenerate. We aim to define developmental gene expression variations among these populations and generate a toolbox of genetic markers to help study these disorders. We used *Islet-1:GFP* and *Hb9:GFP* mice to isolate seven distinct MN pools on embryonic days E10.5 and E11.5 via microdissection and fluorescence-activated cell sorting (FACS): three ocular motor cranial nuclei (CN) affected in CCDDs but preserved in ALS (CN3, CN4, CN6), and four MN types that are affected in ALS as well as in a subset of CCDDs (CN5, CN7, CN12, and spinal motor neurons). RNA-seq analysis was performed on each. Single cell RNA-seq was also done on CN3 and CN4 MNs. Gene expression was validated with database analysis, in situ hybridization, and evaluation of mouse Cre reporter lines. Birthdates of the OMN populations were analyzed via BRDU/EdU injections on different days of development (E8.5-E11.5). RNA-Seq analysis was performed with Genesifter (pooled samples) or SEURAT (single cell data). Each MN population showed unique gene expression patterns, including novel markers of OMNs. Some CN3 subpopulations may correspond to spatially distinct subnuclei and/or temporally distinct populations that are selectively affected in some CCDDs. Overall, these data uncover distinct developmental gene expression patterns and markers of the various cranial motor neurons that provide new tools to study their selective vulnerability in the CCDDs.

Disclosures: **M.F. Rose:** None. **M.A. Tischfield:** None. **A. Gelber:** None. **A.A. Nugent:** None. **P. Ang:** None. **S. Izen:** None. **W. Huang:** None. **R. Satija:** None. **O. Rozenblatt-Rosen:** None. **A. Regev:** None. **E. Engle:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

Support: ANR DECIPHER

ANR DESIRE

Title: Alteration of functional cortical connectivity in a rat model of subcortical band heterotopia

Authors: *V. PLANTIER, F. MARTINEAU, F. WATRIN, E. BUHLER, J.-B. MANENT, I. BUREAU, A. REPRESA
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Abstract: Subcortical band heterotopia (SBH) occurs when neocortical neurons fail to migrate to the correct location and accumulate in the subcortical white matter, close to the lateral ventricle. SBH in humans is associated with mental retardation and intractable epilepsy. The syndrome is mainly related with mutations in the doublecortin (DCX) gene. Previous investigations on a rat model of SBH, the DCX-KD rat, suggest that most interictal-like discharges originate in the normotopic cortex and propagate then to the SBH (Petit, Jalabert *et al.* 2014). In addition to this, cortical neurons overlying the heterotopia were shown to exhibit a massive increase of ongoing glutamatergic synaptic currents (Ackman *et al.*, 2009). We therefore postulate that neuronal networks in normotopic cortex experience a significant remodeling that would contribute to the development of clinical manifestations. To evaluate this hypothesis, wistar rats underwent an *in utero* injection/electroporation at E16 of shRNA constructs targeting DCX to generate a SBH, close to the barrel cortex. Two weeks after birth, the functional connectivity to layer II/III in barrel field cortex was investigated using laser scanning photo stimulation of caged glutamate combined with local field and whole-cell patch clamp recordings. Physiologically, barrel cortex circuits are organized in functional columns spanning multiple layers (L1-L6). Our data clearly show network alterations in the DCX rat model, that diverge depending of the position of the barrel analyzed either above or adjacent to the SBH. In the barrels adjacent to the malformation, the column organization was disturbed and the layer II/III received strong excitatory inputs from layers II/III/IV/V and VI compared with control rat barrel cortex. The inhibitory inputs from the same layers to layer II/III were also increased but to a lesser extent signifying a hyperexcitability of this cortical network in SBH-rats. In contrast to this, the barrels placed directly over the heterotopia displayed a dramatic reduction of the excitatory inputs from layers IV to layer II/III while inhibitory inputs were apparently not modified. These results strongly suggest that the presence of band heterotopia associates a significant reorganization of the normotopic cortex network that would impair the normal operation of somatosensory cortex.

Disclosures: **V. Plantier:** None. **F. Martineau:** None. **F. Watrin:** None. **E. Buhler:** None. **J. Manent:** None. **I. Bureau:** None. **A. Represa:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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KAKENHI JP15H02355

KAKENHI JP15H01586

KAKENHI JP16H06482

Title: Analysis of cortical development in a newly established mouse model of extremely premature infants with brain injuries

Authors: *K.-I. KUBO[1], K. DEGUCHI[1], T. NAGAI[2], A. KITAZAWA[1], K. YOSHIDA[3], W. SHAN[4], M. ARAMAKI[1], K. ISHII[1], M. SHIN[1], Y. MATSUNAGA[1], K. HAYASHI[1], K. F. TANAKA[1], S. TAKASHIMA[5], M. NAKAYAMA[6], M. ITOH[7], Y. HIRATA[1], B. ANTALFFY[8], D. D. ARMSTRONG[8], K. YAMADA[2], K. INOUE[7], K. NAKAJIMA[1]
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Abstract: More than 25,000 extremely preterm infants (EPIs) (children born before 28 gestational weeks [GWs]) are born annually in the United States (approximately 0.6% of all births), and this number is increasing by 7% a year. Although the survival rate of extremely preterm infants has improved, many survivors (25% to 50%) develop cognitive impairment in later life. The reason why cognitive impairment is a common neurological outcome following brain injury in EPIs remains unknown. Moreover, EPIs are more likely to have psychiatric disorders, such as autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder

(ADHD). In this study, we investigated whether altered neuronal migration might be involved in the pathogenesis of the cognitive impairment that often develops later in EPIs with brain injury. We examined the developing human neocortex and confirmed that neuronal migration continues beyond 23 GWs, the gestational age at which the EPIs are born. We observed larger numbers of ectopic neurons in the white matter in human EPIs with brain injury. To investigate whether preterm brain injury affects neuronal migration, we established a mouse model of EPIs with brain injuries by producing ischemic brain damage in mouse embryos with the occlusions of the maternal uterine arteries and analyzed cortical development. The mice showed delayed neuronal migration, ectopic neurons in the white matter, altered neuronal alignment, and abnormal cortico-cortical axonal wiring. Similar to human EPIs brain injury, the surviving mice exhibited cognitive deficits. These findings suggest that altered neuronal migration by brain injury contribute to the subsequent development of cognitive impairment in EPIs.

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Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

Support: NIH 1P20GM103653-01A1

NIH P20GM103446

Title: Effect of bilateral asymmetry on neuronal connectivity and behavior

Authors: *P. HAN[1], M. D. MERSHA[2]
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Abstract: Animal body plans tend to display external symmetry; however, their internal organs can be anatomically and/or functionally asymmetrical. Visceral organs such as liver, pancreas, lungs etc. show anatomical asymmetry in a bilateral fashion. Left and right cerebral hemispheres are functionally asymmetric and small deviations have been correlated with pathologies such as schizophrenia and bipolar disorders. Bilateral asymmetry is genetically and developmentally defined as a third axis besides the anterior/posterior and dorsal/ventral axes. We are using *Caenorhabditis elegans* as a model to study the molecular genetic bases of left/right (L/R)

asymmetry. Externally *C.elegans* is predominantly symmetrical but the animal displays clear bilateral asymmetry in the viscera in terms of the gut and gonad placement. In addition, certain neuronal pairs also show asymmetry such as the left and right neurons of the AWC neuronal pair. Mutants affecting early development and spindle orientation have been reported to result in bilaterally reversed embyos, and deletion of a Gα protein coding gene expressed at the 4-6 cell stage has been shown to yield up to 50% sinistral worms. We are looking at initial or early symmetry-breaking steps by recording the rate of sinistral embryos, lethality rates, and the behavior of surviving adults. Our results with various mutants show that surviving adults are impaired in both associative and non-associative learning. We are currently focusing on whether the reversed asymmetry directly correlates with the observed effects on behavior, and mapping potentially atypical neuronal circuits.
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Disclosures: P. Han: None. **M.D. Mersha:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

Support: Explorer Award, Simons Foundation Autism Research Initiative (IMR)

Dana Foundation Program in Clinical Neuroscience Research (IMR)

Provost's Undergraduate Research Award (AS)

Title: An optogenetics based approach for elucidating how high frequency stimulation at the subthalamic nucleus suppresses excessive self-grooming in autism-like mouse models

Authors: *A. STEPANIAN[1], S. ADHIKARI[1], A. D. CHANG[1], J. S. CHUNG[1], V. A. BERGES[1], G. Y. FRIDMAN[2], J. M. BARABAN[3], I. M. RETI[1]
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Abstract: Approximately one quarter of individuals with an autism spectrum disorder (ASD) display self-injurious behavior (SIB) ranging from head banging to self-directed biting and punching. Electroconvulsive therapy (ECT) can yield up to 90% suppression of SIB frequency; however, these patients typically require frequent maintenance ECT to sustain the improvement gained during the acute course. Long-term consequences of such frequent M-ECT started as early as childhood in some cases are unknown, and there is a need for alternative forms of

chronic stimulation for these patients.
It has been shown that high frequency stimulation at the subthalamic nucleus (STN-HFS) significantly suppresses excessive self-grooming in *Shank3B*$^{-/-}$ mice. Since STN-HFS stimulates both neurons at the STN and fibers of passage that pass adjacent to this nucleus, it is unclear which pathways mediate the acute and persistent suppression of excessive self-grooming by STN-HFS. As it would be important to distinguish between these two mechanisms before considering invasive or non-invasive neuromodulation for patients, we are utilizing an optogenetics-based approach to help determine which pathways mediate the response. We are conducting electrophysiological studies optically stimulating mice at the STN that have been light sensitized by injection of channelrhodopsin (ChR) in the STN or cortical regions that send fibers of passage adjacent to the STN.
Field recordings at the STN with stimulation at 5Hz intervals (5mW, 2ms for 3s) demonstrate near complete spike entrainment at up to 15Hz, before falling at higher frequencies. Using the same stimulation parameters, we evaluated the response to continuous optical stimulation at 15Hz for an hour, and observed almost 100% spike entrainment for the entire duration of the test (n=3).
For fibers of passage, mice were injected in M2 with ChR and 3 weeks later field recordings were made at M2 in response to optogenetic activation at STN. We firstly conducted "collision tests" to demonstrate that the selected field at M2 contains neurons that project to fibers of passage adjacent to the STN. Field recordings at M2 at 5Hz intervals (5mW, 2ms for 3s) demonstrate near complete spike entrainment at up to 8Hz, before falling at higher frequencies. We observe nearly 100% spike entrainment to one hour of continuous optical stimulation at 7 Hz.
We will use this data to guide stimulation parameters for ongoing behavioral experiments, where animals will receive fiber optic implants at either light sensitized STN or M2 (to stimulate fibers of passage). A self-grooming assay will be employed to quantify changes in self grooming following bouts of stimulation.

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Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Support: University of Florida CTSI Pilot Project Award

APA Dissertation Research Award

Title: Mapping the neural circuitry of restricted repetitive behavior: Multimodal neuroimaging in an animal model

Authors: *M. H. LEWIS[1], ***M. H. LEWIS**[1], B. J. WILKES[2], C. BASS[2], H. KORAH[2], M. FEBO[1]
[1]Psychiatry, UF Col. of Med., Gainesville, FL; [2]Psychology, Univ. of Florida, Gainesville, FL

Abstract: Restricted, repetitive behavior is diagnostic for autism spectrum disorder (ASD) and a prominent feature of other neurodevelopmental disorders. Our lab utilizes an inbred mouse strain (C58) that exhibits robust repetitive motor behavior phenotype (vertical jumping, backward somersaulting). Previous histochemical work from our lab suggests that alterations in basal ganglia circuitry mediate the expression of this repetitive behavior. Neuroimaging studies in ASD also support the role of altered basal ganglia circuitry in repetitive behavior, but also suggest that the cerebellum may be involved. In order to further investigate the role of basal ganglia and cerebellar circuitry alterations in repetitive behavior, we performed *ex vivo* magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) on C58 mice (n=10) and C57BL/6 controls (n=10) reared in standard housing conditions. We performed whole brain voxel-based morphometry (VBM), as well as targeted investigations of volume and fractional anisotropy (FA) in the basal ganglia and cerebellum. We also performed probabilistic tractography to assess intra-basal ganglia connectivity. As with prior work in our lab, we found high rates of repetitive motor behavior in C58 mice, with little such repetitive behavior exhibited by C57BL/6 control mice. Consistent with our hypothesis of indirect pathway dysfunction, to date we have found significant alterations in basal ganglia morphology among C58 mice, including smaller volumes of the globus pallidus and subthalamic nucleus, as well as reduced FA in WM fiber tracts within the basal ganglia. These findings provide novel evidence for alterations in basal ganglia morphology in the C58 animal model of repetitive behavior, and are consistent with human neuroimaging findings of altered basal ganglia morphology in relation to repetitive behavior in ASD.

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Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Support: Lou Lou Foundation

Hope4Harper

Title: Hippocampal-specific ampa receptor dysregulation in cdkl5 ki mice

Authors: *M. YENNAWAR[1], R. WHITE[2], F. E. JENSEN[2]
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Abstract: CDKL5 disorder is a rare neurological disease where patients develop severe seizures, followed by intellectual disability and autistic behaviors. It results from loss-of-function mutations in the gene for cyclin-dependent kinase-like 5 (CDKL5). There are several mouse models of CDKL5 disorder where mice exhibit autistic-like behaviors but not spontaneous seizures. In our investigation of the CDKL5 knock-in (KI) mouse, we previously reported that the mice have deficits in learning, memory and social interaction, as well as motor neuron dysfunction. We now show that adult CDKL5 KI mice have a significantly lower seizure threshold than WT littermates after being administered a subthreshold dose of pentylenetetrazol (n=10, p=0.0099). To investigate the molecular changes underlying the hyperexcitability in CDKL5 KI mice, we performed Western blot analysis of membrane-bound proteins that regulate the excitatory-inhibitory (E-I) balance. We found that the ratio of AMPA receptor subunits GluA2:GluA1 is significantly lower in CDKL5 KI hippocampus compared to WT littermates (n=10, p= 0.0048), and is driven by decreased levels of GluA2 (n=14, p=0.0129). There were no significant changes in NMDA receptor or $GABA_A$ receptor subunits. Decreased GluA2:GluA1 is consistent with the literature of E-I imbalance and suggests that there is an increase in the number of GluA2-lacking, Ca^{2+} permeable (CP) AMPA receptors at the membrane. Increased levels of CP-AMPARs cause alterations in Ca^{2+} homeostasis, and may result in hyperexcitability and altered plasticity. Ongoing electrophysiology experiments are being performed to elucidate the functional consequence of dysregulated AMPA receptors in CDKL5 KI mice. These novel results indicate that molecular changes in the hippocampus of CDKL5 KI mice may underlie the lowered seizure threshold and hippocampal-specific behavioral abnormalities observed in these mice.

Disclosures: **M. Yennawar:** None. **R. White:** None. **F.E. Jensen:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

Support: AG042178

AG047812

Garrison Family Foundation

Title: Oxidative stress and mitochondrial dysfunction in TALLYHO/JngJ mice - a common link between type 2 diabetes, obesity and Alzheimer's disease

Authors: *J. S. BHATTI[1,2], K. THAMARAI KANNAN[3], P. REDDY[1]
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Abstract: Recent studies linked the high prevalence of type 2 diabetes mellitus (T2DM) and obesity with the risk of dementia and Alzheimer's disease (AD). However, the molecular mechanisms linking T2DM and AD are unknown. The present study was aimed to study the biochemical and mitochondria/oxidative stress biomarkers in a mouse model of T2DM, TALLYHO/JngJ (TH). Age and sex matched, SWR/j mice were used as non-diabetic and non-obese control mice. We studied the development of T2DM and obesity in TH mice at 8, 16 and 24 weeks of age by measuring body weight, glucose tolerance, insulin tolerance, and triglyceride levels in TH and SWR mice. Oxidative stress and mitochondrial markers were studied after the development of T2DM in TH and control mice. Compared with age- and sex-matched control mice, both male and female TH mice were significantly heavier, and hyperinsulinemic. The hyperinsulinemia was more prominent in male TH mice than female TH mice. Plasma glucose levels progressively increased with age in male TH mice resulting in type 2 diabetes, while female TH mice remained normoglycemic throughout the study. Interestingly, male TH mice demonstrated a severe increase in plasma triglyceride levels in the pre-diabetic stage that was maintained throughout the study. Oxidative stress and mitochondrial dysfunction were observed in diabetic male mice compared to control, female TH mice. The histopathological examinations show that both the male and the female TH mice had enlarged pancreatic islets compared to control mice. In conclusion, these findings suggest that insulin resistance, hypertriglyceridemia and hyperglycemia causes oxidative stress which then leads to mitochondrial dysfunction in TH mice. Based on these observations, we conclude that TH mice can be used as a relevant model to study the molecular links between type 2 diabetes and Alzheimer's disease.
Keywords: Type 2 diabetes mellitus; TallyHo mice; Oxidative stress; Alzheimer's disease

Disclosures: J.S. Bhatti: None. **K. Thamarai Kannan:** None. **P. Reddy:** None.

Poster

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Autism Speaks Postdoctoral Fellowship 8679

FRAXA Postdoctoral Fellowship

Title: Decreased rates of cerebral protein synthesis measured *In vivo* in a mouse model of tuberous sclerosis complex: Influence of recycling of amino acids derived from protein breakdown

Authors: R. M. SARE[1], T. BURLIN[1], T. HUANG[1], *D. PICCHIONI[2], C. B. SMITH[1]
[1]Section on Neuroadapatation and Protein Metabolism, Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Intramural Res. Program, NIH, Bethesda, MD

Abstract: Tuberous Sclerosis Complex (TSC) is an autosomal dominant neurogenetic disorder affecting 1 in 6,000 people. TSC usually has effects on the central nervous system manifested by a high incidence of seizures, intellectual disability, and autism. TSC is caused by mutations in either *TSC1* or *TSC2*, which encode for proteins that form a complex and interact with a small GTP-binding protein, RHEB, to inhibit mammalian target of rapamycin complex 1 (mTORC1). mTORC1 is a central regulator of ribosomal biogenesis and translation initiation. We investigated the effects of *Tsc2* haploinsufficiency ($Tsc2^{+/-}$) on regional rates of cerebral protein synthesis (rCPS) measured *in vivo* by means of the L-[1-^{14}C]leucine method. This method is based on the quantitative autoradiographic determination of the amount of labeled product formed (labeled protein) divided by the integrated specific activity of the tissue leucine pool for protein synthesis. There are two possible sources of leucine in the precursor pool: plasma and protein degradation. In this method, the fraction of leucine derived from arterial plasma (lambda) is included in the calculation. In our initial evaluation, we assumed that the value of lambda was unchanged in $Tsc2^{+/-}$ mice, and with this assumption, we found diminished rCPS in freely-moving, awake, male $Tsc2^{+/-}$ mice at 3 months of age. To confirm the validity of this unexpected decrease, we measured lambda in a separate series of WT and $Tsc2^{+/-}$ mice. In the $Tsc2^{+/-}$ animals, the value of lambda is higher compared with WT mice indicating that in $Tsc2^{+/-}$ mice a greater fraction of the precursor pool comes from plasma and a smaller fraction comes from protein breakdown. This substantiates the changes in rCPS that we observed and suggests that the rates of both protein synthesis and protein degradation are decreased. Our results indicate a complex role of mTORC1 in the regulation of cerebral protein synthesis.

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Poster

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Title: Evaluating the role of cohesin complex proteins in memory and learning

Authors: *K. A. EDWARDS[1], B. Z. KACSOH[1], M. B. HOPPA[2], G. BOSCO[1]
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Abstract: Mutations in proteins that organize chromatin are often found in neurological diseases, such as Cornelia de Lange Syndrome (CdLS). However, the mechanisms linking chromatin organizers to neurological defects remain unclear. CdLS patients present with microcephaly, intellectual disability, and memory deficits caused by heterozygous loss-of-function mutations in the genes encoding the cohesin complex proteins and the protein that loads cohesin onto chromatin, Nipped-B (NipB). These proteins function together in regulating chromatin structure and gene transcription. Our objective is to determine how cohesin and cohesin-related proteins regulate memory, learning and social behavior in *Drosophila*. In a non-associative social learning and memory paradigm, we can measure how mutations in cohesin or NipB are able to remember and learn. We found that mutations in SMC1, a cohesin protein, impaired memory formation while flies with mutations in NipB have impaired memory retention. Additionally, flies with mutations in Rad21, another cohesin protein, are unable to learn while flies with mutations in SMC1 and NipB have an impaired ability to learn. We are continuing to investigate these phenotypes to evaluate how cohesin and cohesin-related proteins influence memory and learning in adult organisms.

Disclosures: K.A. Edwards: None. **B.Z. Kacsoh:** None. **M.B. Hoppa:** None. **G. Bosco:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 653.14/C26

Topic: A.07. Developmental Disorders

Support: R01-NS097537

Title: Hyperactivation of ERK/MAPK leads to altered cortical projection neuron outgrowth, reduced activity dependent gene expression, and motor learning deficits

Authors: *G. R. BJORKLUND[1], L. T. HEWITT[2], K. NISHIMURA[1], J. M. NEWBERN[1]
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Abstract: A series of well-defined genetic mutations found within the RAS/RAF/MEK/ERK (ERK/MAPK) pathway are the source of syndromes collectively known as RASopathies. A majority of these syndromes result in the upregulation of ERK/MAPK signaling and are linked to intellectual disability and developmental delay. However, it is unknown whether altered cortical connectivity and abnormalities in axonal development contribute to these neurological defects. Additionally, cortical layer and neuron type specific effects on developmental connectivity, motor function, and learning have yet to be investigated fully. Here, we have used a conditional genetic approach to hyperactivate the ERK/MAPK pathway in glutamatergic neurons of the developing mouse cortex. We have found that constitutive activation of MEK1 in glutamatergic neurons across all cortical layers leads to reduced corticospinal elongation and learning deficits in rotarod and skilled reaching and grasping tasks. Moreover, our data indicates this coincides with a reduction in activity-dependent Arc and c-Fos expression throughout the motor cortex. Our experiments will examine whether these behavioral deficits are also linked to altered corticostriatal or callosal projection neuron outgrowth. We have additionally tested whether the changes in axonal outgrowth are due to layer 5 autonomous effects of constitutively active MEK1 using Rbp4:Cre mice. Importantly, we find that the alteration in corticospinal connectivity is indeed layer 5 autonomous. These mutants also exhibit a significant reduction in corticostriatal and callosal innervation. We have not found that these axonal outgrowth phenotypes coincide with changes in rotarod performance and are currently assessing skilled reaching and grasping and activity dependent gene expression. This data suggests that motor learning deficits are not due solely to hyperactivation of ERK/MAPK in glutamatergic neurons in layer 5. Nonetheless, our data demonstrates an important layer 5 autonomous role for MEK1 hyperactivation in modulating long-range axonal connectivity. These findings may provide insight into candidate pathological mechanisms that drive neurological defects in RASopathies.

Disclosures: G.R. Bjorklund: None. **L.T. Hewitt:** None. **K. Nishimura:** None. **J.M. Newbern:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Program#/Poster#: 653.15/C27

Topic: A.07. Developmental Disorders

Support: NIH P01 HD083157

Title: Ranbp1 haploinsufficiency contributes to cranial neural crest anomalies in 22q11.2 DS

Authors: *T. M. MAYNARD, E. M. PARONETT, C. A. BRYAN, J. A. SABATINO, B. A. KARPINSKI, A. FERNANDEZ, A. S. LAMANTIA
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Abstract: 22q11.2 Deletion Syndrome (22q11 DS) is a neurodevelopmental disorder that impacts 1 in 4,000 live births. Craniofacial anomalies, including cleft palate and other structural defects of the palate, as well as defects in sensory/motor coordination that impair speech and swallowing, are apparent in most individuals carrying with 22q11.2 deletions. We have found that *Ranbp1*, a 22q11.2 DS candidate gene, is a key regulator of multiple aspects of craniofacial development. Mice with homozygous null mutations of *Ranbp1* have a severe, strongly penetrant cleft palate phenotype, with a complete failure of palatal closure, and a concomitant failure to form key neural-crest derived palatal bone structures including the palatal processes of the maxilla and premaxilla. Conditional neural-crest specific knockout of *Ranbp1* yields a highly-penetrant but less-severe phenotype: *Wnt1*-Cre::*Ranbp1* null embryos have closed but highly dysmorphic palatal structure. *Ranbp1* mutation also disrupts the formation of the trigeminal ganglion, mirroring anomalies we have observed in the *LgDel* mouse model of 22q11 DS. Heterozygous *Ranbp1* mutants display a more subtle and variable phenotype: heterozygous mutants show a delay in palatal shelf elevation/extension, as closure appears to be complete in most by E15.5. This delay appears to prefigure minor anomalies in palatal bone structure that are apparent at E17.5, and is accompanied by other subtle craniofacial anomalies. Thus, *Ranbp1* appears to be the first 22q11.2 candidate gene that is able to heterozygously compromise palate formation, as well as disrupt the development of other craniofacial structures, possibly by disrupting the function of key craniofacial signals that pattern the cranial neural crest.

Disclosures: T.M. Maynard: A. Employment/Salary (full or part-time):; George Washington University. **E.M. Paronett:** A. Employment/Salary (full or part-time):; George Washington University. **C.A. Bryan:** A. Employment/Salary (full or part-time):; George Washington University. **J.A. Sabatino:** A. Employment/Salary (full or part-time):; George Washington University. **B.A. Karpinski:** A. Employment/Salary (full or part-time):; George Washington University. **A. Fernandez:** A. Employment/Salary (full or part-time):; George Washington University. **A.S. LaMantia:** A. Employment/Salary (full or part-time):; George Washington University.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

Support: H2020 ITN 643051

Title: Latrophilin 3: A mouse model of attention deficit hyperactivity disorder

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Abstract: Attention Deficit Hyperactivity Disorder (ADHD) may be defined as a chronic condition marked by persistent inattention, hyperactivity and sometimes impulsive behaviour. ADHD begins in childhood and persists into adulthood in up to two thirds of cases. Animal models are essential for understanding this disorder. Multiple polymorphisms in the *LPHN3* gene have been repeatedly linked with an increased risk of ADHD, making it an attractive target for modelling in genetically modified organisms. Latrophilin 3 is produced by neuronal cells, localised at synapses and has putative roles in neuronal migration and synapse development. *Lphn3*-deficient mice may incorporate some key attributes of ADHD. Promisingly, previous studies in *Lphn3* -/- mice have reported increased locomotive activity and altered gene expression of dopaminergic and serotoninergic receptors and transporters.

In this study we examine the characteristics of *Lphn3*-deficient mice in multiple behavioural domains. 19 *Lphn3* -/- mice, 20 *Lphn3* +/- mice and 29 *Lphn3* +/+ mice were tested in the open field (OF), light dark box (LDB), object recognition (OR) and Barnes Maze (BM) tasks for respective abnormalities in locomotive activity, anxiety level, recognition memory and spatial memory. A subgroup of *Lphn3* -/- and *Lphn3* +/+ were tested in the social interaction (SI) and resident intruder (RI) paradigms for alterations in sociability and aggression. *Lphn3*-deficient mice's movement parameters were tested in the novel Gaitlab System.

The OF Test has confirmed the increased *Lphn3* -/- locomotive activity phenotype (one way ANOVA p=0.0001). Contrasting this increased horizontal locomotive activity is a drastically reduced rearing activity (one way ANOVA p=0.0001). A reduction in recognition memory of *Lphn3* -/- mice was observed in the OR task (one way ANOVA p=0.004) along with reduced spatial memory and learning ability in the BM test (two-way repeated measures ANOVA p=0.0039). In the RI paradigm *Lphn3* -/- mice displayed dramatically reduced aggression levels with a complete absence of attacks in the 8 null mice tested (Fisher's Exact Test p=0.0007). Despite this reduction in aggression, initial analysis of *Lphn3* +/+ and -/- mice in the SI task has not revealed any significant differences in sociability or social memory. Movement analysis described altered limb positioning of *Lphn3* -/- mice in comparison to *Lphn3* +/+ mice. *Lphn3* +/- mice were not found to be significantly different from WT mice in any of the behavioural paradigms chosen for study.

These findings confirm the Lphn3 null mouse as a promising model of ADHD, which is currently being further expanded upon by molecular analysis including RNA-sequencing.

Disclosures: **N. Mortimer:** None. **M. Ribases:** None. **J. Ramos-Quiroga:** None. **K. Lesch:** None. **O. Rivero:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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AES Grant 367394

Title: Ablation of Arx in mature GABAergic interneurons impaired network function via dysfunction of calcium extrusion and sequestration mechanisms in the mouse hippocampus

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Abstract: Transcription factors (TFs) establish the molecular codes that regulate early developmental stages of GABAergic interneurons. The Aristaless Related homeobox (*Arx*) protein is a TF within such regulatory network controlling interneuron development. However, *Arx* remains expressed in mature interneurons, suggesting a divergent, yet unknown, function. We previously showed that postnatal ablation of *Arx*, in interneurons, impaired long term plasticity (LTP) in the hippocampus. Preliminary investigation into the molecular mechanisms mediating these effects suggest a dysregulation in homeostatic basal Ca^{2+} levels. Here, we further investigated the molecular pathways involved in this dysregulation of basal Ca^{2+} levels. To temporally control *Arx* expression, we crossed a floxed *Arx* mouse ($Arx^{fl/fl}$) with a tamoxifen (Tam) inducible Cre^{ER}- mouse, resulting in complete loss of *Arx* 30 days after Tam injection. We reasoned that if changes in homeostatic Ca^{2+} levels is the main factor limiting LTP expression, then elevation of external Ca^{2+} or chelation of excess intracellular Ca^{2+}, or activation of Ca^{2+}extrusion and sequestration pumps could reverse these deficits and rescue LTP. Thus, we recorded field excitatory postsynaptic potentials (fEPSPs) at CA1 synapses in response to Schaffer collaterals (SC) stimulation in $Arx^{+/y}$ and $Arx^{-/y}$; Cre^{ER} mice in normal recording solution, in high extracellular Ca^{2+}, in BAPTA-AM, or in the plasma membrane Ca^{2+}-ATPase pump (PMCA) agonist Phosphatidylinositol 4,5-bisphosphate (PIP2). To measure LTP, baseline fEPSPs were recorded for 30 min in normal solution with last 10 min of recordings in presence or absence of the aforementioned drugs and post-tetanus fEPSPs were recorded in normal conditions.
Our results show that $Arx^{-/y}$; Cre^{ER} mice had reduced LTP and confirmed our preliminary observation that perfusion with higher external [Ca^{2+}] during induction partially restored CA1 LTP to $Arx^{-/y}$ slices. This rescue of LTP in $Arx^{-/y}$ slices was also noted when Ca^{2+} influx was partially blocked by reducing the extracellular Ca^{2+}/Mg^{2+} ratio. BAPTA-AM completely restored

LTP to *Arx*$^{-/y}$ slices. Preliminary results show that pre-application of PIP2 completely restored CA1 LTP in these *Arx*$^{-/y}$ slices. Finally, direct activation of CaMKII in *Arx*$^{-/y}$ slices rescued LTP deficits in 60% of the slices tested.
Our results suggest that postnatal loss of *Arx* elevated postsynaptic Ca^{2+} levels due to impairments of Ca^{2+} extrusion pumps to ultimately limit SC-CA1 LTP. These data suggest that modulation of Ca^{2+} buffering capacity or PMCA pump activity may be temporally targeted for therapy in patients with *Arx* mutations and more broadly in epilepsy.

Disclosures: D.J. Joseph: None. **A.J. McCoy:** None. **R. Risbud:** None. **E.D. Marsh:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

Support: NIH Grant EY021222

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Title: CASK haploinsufficiency produces developmental retinal ganglion cell pathology and optic nerve hypoplasia

Authors: *A. KERR, C. LIANG, K. MUKHERJEE, M. A. FOX
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Abstract: Optic Nerve Hypoplasia (ONH) is currently the leading cause of childhood blindness in developed nations and its prevalence has been rising steadily over the past decades. Despite its prevalence, we know little about the genetic, molecular, or cellular mechanisms underlying ONH. A previous study described ONH in a cohort of patients with mutations in the X-linked gene CASK. CASK encodes a membrane-associated guanylate kinase (MAGUK) protein with well-established roles in neural development and synaptic function. In addition to ONH, CASK mutations are associated with microcephaly with pontine and cerebellar hypoplasia (MICPCH), X-linked intellectual disability (XL-ID), and autism spectrum disorder. Our previous studies demonstrated that heterozygous deletion of CASK in female mice recapitulate many of the phenotypes observed in patients with CASK mutation, including ONH. Thus, heterozygous CASK mutant mice represent a novel model to gain mechanistic insight into the development and pathogenesis of ONH. Here, we sought to use this model to assess changes in the subcortical visual system in CASK(+/-) mice and, as expected, our results demonstrate that fewer retinal axons are present in the developing optic nerve of CASK(+/-) mice. However, it is important to note that reduced optic nerve (ON) size and retinal axon number are not observed at birth, but

emerge during perinatal development. Accompanied with changes in the ON, we observed reduced retinogeniculate connectivity and a reduction in retinal ganglion cells (RGCs) in these mutants. These are the first results to demonstrate a role for CASK in the development of the subcortical visual development, and they demonstrate that disruption in CASK signaling represents a novel model for investigating mechanisms underlying ONH. For example, we are now using conditional approaches to delete CASK in specific population of cells in the retina, ON, and brain to elucidate cellular mechanisms underlying ONH.

Disclosures: A. Kerr: None. **C. Liang:** None. **K. Mukherjee:** None. **M.A. Fox:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

Title: Defective heterochromatin remodeling due to Nde1 loss leads to nuclear architecture aberration of cortical neurons

Authors: *Y. FENG, *Y. FENG, ***Y. FENG**, A. LANCTOT, Y. GUO
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Abstract: The *NDE1* gene encodes a scaffold protein essential for CNS development. Homozygous loss of *NDE1* results in extreme microcephaly and profound mental retardation, while single nucleotide mutations and copy number variants of its locus 16p13.11 are linked to a wide range of neuro-developmental disorders, suggesting that NDE1 aberrance may underlie polymorphic genetic variations and heterogeneous impairments of brain function. Using murine models of Nde1 mutation, we identified a pivotal role of Nde1 in maintaining the genome stability of cortical neural progenitors through facilitating DNA replication and de novo epigenetic modification of the constitutive heterochromatin. We showed that cerebral cortical neurogenesis is concomitant with substantial heterochromatin compression that was compromised by Nde1 deficiency, leading to high levels of DNA double strand breaks in neural progenitors and profound nuclear architecture aberrations in cortical neurons. The genome and epigenome defects in Nde1 deficient neurons were heterogeneous and shared the hallmarks of malignant transformation and degeneration. These results demonstrate that NDE1-depedndent heterochromatin remodeling is indispensable for chromosome structure and genome integrity of cortical neurons.

Disclosures: Y. Feng: None. **Y. Feng:** None. **A. Lanctot:** None. **Y. Guo:** None.

Poster

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Topic: A.07. Developmental Disorders

Support: NINDS 1R01NS097537-01

Title: Functions of ERK/MAPK signaling in GABAergic neuron development and identity

Authors: *M. HOLTER[1], G. R. BJORKLUND[1], S. A. SHAH[1], J. D. NICHOLS[2], J. S. MARTINEZ[1], T. R. ANDERSON[3], J. M. NEWBERN[1]
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Abstract: Perturbations to ERK/MAPK signaling give rise to a family of developmental syndromes, collectively termed RASopathies. Patients with RASopathies exhibit a range of neurological symptoms that include intellectual disability, motor delay, and seizures. Cortical GABAergic neurons are thought to contribute to abnormal neurological function, however, the function of canonical ERK/MAPK signaling in GABAergic neuron development remains poorly understood. To address these questions, we developed transgenic mouse models to induce gain-of- or loss-of-function ERK/MAPK signaling specifically in mouse GABAergic neurons. Our data shows that gain-of-function ERK/MAPK signaling in GABAergic neurons led to the selective loss of fast-spiking parvalbumin-positive GABAergic neurons in the adult mouse cortex. Interestingly, we observed reduced GABAergic neuron number in late embryonic stages of mouse brain development. Studies are underway to determine whether this loss is due to altered GABAergic neuron migration from the ganglionic eminences or early cell death of immature neurons. To reverse GABAergic neuron loss, pharmacological normalization of ERK/MAPK signaling with the MEK inhibitor, PD0325901, is being evaluated. Surprisingly, loss-of-function ERK/MAPK mutations did not yield a comparable degree of GABAergic neuron loss. However, high throughput sequencing of RNA immunoprecipitated from cortical GABAergic neurons harboring mutations to induce loss-of-function ERK/MAPK signaling revealed changes in the expression of various genes important for neuronal differentiation. Whole-cell patch clamp of GABAergic neurons in the juvenile loss-of-function cortex indicated altered physiological properties in fast-spiking neurons that may be explained by changes in connectivity. To fully appreciate these physiological alterations, we have conducted 3D morphological reconstructions to further examine the functional role of ERK/MAPK in GABAergic neuron dendritic outgrowth and activity dependent neuronal development. Continued study of ERK/MAPK signaling in GABAergic neurons will better our understanding

of GABAergic neuron development and mutation specific aspects of RASopathy neuropathogenesis.

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Poster

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Topic: A.07. Developmental Disorders

Support: KAKENHI #26430020

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KAKENHI #15H06538

Title: Caspar-positive area decrease and dendritic morphological change in the sensorimotor cortex are related to motor coordination dysfunction in neonatal white matter injury model rat

Authors: *Y. UEDA[1], Y. BANDO[2], S. MISUMI[1], A. ISHIDA[1], H. HIDA[1]
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Abstract: We established a neonatal white matter injury (WMI) model (Mizuno et al, Neonatology, 2008). The model has slight difficulty in motor coordination without neuron cell loss, which accompanied with oligodendrocyte progenitor cell loss and dysmyelination in the sensorimotor cortex (Misumi et al, Cell Transplantation, 2016). To clarify a question why the motor deficits are induced in our model with no apparent neuron loss, we focused on the histological changes in the sensorimotor cortex. The model was made by right common carotid artery occlusion followed by 6% oxygen for one hour in P3 Wistar rat. Coronal sections in the hindlimb motor cortex (M1) were prepared from adult model rat and processed for the immunostaining. We used contactin associated protein 1 (Caspr) antibody to detect dysmyelination and Golgi-staining to see dendritic morphological alterations. Caspar staining revealed that the positive particle was usually detected as twin-dots and the number of Caspr positive particles was decreased in the H-I side cortex, where less staining of myelin basic protein was shown in our previous data. Golgi-staining revealed that the neurite morphology was different between H-I side and contralateral side. Furthermore, the more dendritic extension was observed in the H-I side of the cortex. These data suggest that the slight difficulty in motor

coordination with no obvious neuron loss in a neonatal WMI model was probably related to less number of Caspr particles and altered dendritic extensions in the H-I sensorimotor cortex.

Disclosures: **Y. Ueda:** None. **Y. Bando:** None. **S. Misumi:** None. **A. Ishida:** None. **H. Hida:** None.

Poster

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Title: Trio protein haploinsufficiency causes neurodevelopmental disease-associated deficits

Authors: *S. M. KATRANCHA[1,2,3], Y. WU[4], M. ZHU[7], B. A. EIPPER[5,6], R. E. MAINS[5], A. J. KOLESKE[1,2,3]
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Abstract: Bipolar disorder, schizophrenia, autism, and intellectual disability are complex neurodevelopmental disorders that debilitate approximately 2.6%, 1.1%, 1.5%, and 1.0% of individuals in the United States, respectively, and millions more worldwide. For each disorder, genetic and environmental risk factors disrupt normal cognition and alter neuronal connectivity, as exemplified by alterations in dendrite and dendritic spine structure. Studies in diverse model organisms have described important roles for the 330 kDa triple functional domain (TRIO) protein in the regulation of dendrite, dendritic spine, and synapse development and function. TRIO mRNA is alternatively spliced, generating isoforms containing combinations of 2 guanine nucleotide exchange factor (GEF) domains and 1 putative kinase domain. A targeted search of the literature reveals that the *TRIO* gene has a significant number of neurodevelopmental

disease-associated *de novo* mutations. A majority of the *de novo* mutations are found in the first GEF domain (GEF1), which activates Rac1, a small GTPase. To determine the impact of these *de novo* mutations and other rare disease-associated variants on TRIO function, we expressed wild type and mutated TRIO protein in HEK293 cells and used a Rac1 biosensor to assay its Rac1 GEF activity. We discovered that 2 TRIO GEF1 mutants had significantly decreased ability to activate Rac1, compared to wild type. To study the behavioral impact of damage to one TRIO allele, we created mice heterozygous for *Trio* deletion in excitatory neurons of the cortex and hippocampus. These mice along with sex-matched, wild type littermates were evaluated using a variety of behavioral tests. Mice heterozygous for *Trio* in excitatory neurons exhibit increased anxiety-like behavior, decreased locomotor activity, and deficits in sociability. Western blot analysis of cortical extracts demonstrated that levels of Trio protein were reduced to approximately half of wild type levels in the heterozygotes. In summary, disease-associated *de novo* mutations decrease TRIO's GEF activity toward Rac1, and haploinsufficiency of *Trio* in excitatory neurons produces deficits with close parallels to neurodevelopmental disorders.

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Poster

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HD090260

Title: Neurodevelopmental deficits and seizure susceptibility in conditional double heterozygous Crk and CrkL telencephalic-specific knockouts

Authors: *A.-M. KATSAROU[1], C. A. BLACKWOOD[2], O. SHANDRA[1], W. B. MOWREY[3], S. NANDI[2], J. M. HÉBERT[2], A. S. GALANOPOULOU[4]
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Korey Dept Neurology, Dominick P Purpura Dept Neuroscience, Einstein/Montefiore Epilepsy Cntr, Albert Einstein Col. Med., Bronx, NY

Abstract: Background: Deletions of chromosomal loci that include the *Crk* and *Crkl* genes, *coding for signaling adapters,* have been linked to syndromes that may manifest with abnormal brain development, intellectual disability and seizures but also non-neurological symptoms. *Crk* may be part of the 17p13 deletion seen in Miller-Dieker syndrome (MDS), while *Crkl* is included in the deleted 22q11.2 region in DiGeorge syndrome (DGS). The contribution of *Crk* genes to the neurological phenotypes of these syndromes has not been fully investigated in mouse models.
Objective: To determine if *Foxg1*^{Cre}-driven deletion of *Crk* /*Crkl* in mouse telencephalon results in neurodevelopmental defects and increased seizure susceptibility, as seen in MDS and DGS.
Methods: Foxg1^{Cre}-driven deletion of Crk and CrkL was done in *Crk*^{flox} and *Crkl*^{flox} male and female mice. Littermate control and *Crk*+/-; *Crkl*+/- mice were compared blinded to genotype. Body weights, surface righting time (SRT) and open field activity (OFA) were scored between PN3-19. Barnes Maze test of visuospatial learning and memory was done between PN16-19. Two-hour video-monitoring sessions (PN4-5) were scored for spasms. Separate cohorts were monitored with epidural video-EEG for spontaneous seizures.
Results: *Foxg1*^{Cre}-driven *Crk*+/-; *Crkl*+/- mutants had slower weight gain rates (0.20g/d, n=5) than controls (0.28 g/d, n=20) (P=0.01) and higher failure rates in OFA (60% vs 42.8%, P=0.006) and NG (21.3% vs 9.7%, P=0.004). *Crk*+/-; *Crkl*+/- mutants (n=5) had higher failure rates in the Barnes maze test than controls (n=20) (P=0.02). There were no genotypic differences in the frequency of behavioral spasms between PN4-5. Increased threshold to clonic (P=0.03, median test), but not tonic, flurothyl-induced seizures was noted in PN36-39 *Crk*+/-; *Crkl*+/- (n=4) compared to controls (n=20). Video-EEG monitoring revealed disorganized background (2/2), focal frontal epileptic discharges (2/2) and frontal-onset spontaneous seizures (1/2) in the *Crk*+/-; *Crkl*+/- mice but not in controls (n=4).
Discussion: Conditional *Foxg1*^{Cre}-driven *Crk*+/-; *Crkl*+/- loss in mouse telencephalon could lead to neurodevelopmental, visuospatial learning defects. Although no increased susceptibility to flurothyl seizures was seen, *Crk*+/-; *Crkl*+/- showed spontaneous focal epileptic discharges and/or seizure suggesting a trend towards epilepsy phenotype.
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Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

Support: the Grant-in-Aid for Scientific Research C Grant Number 25461778

Title: Social isolation during the critical period reduces synaptic and intrinsic excitability of a subtype of pyramidal cell in mouse prefrontal cortex

Authors: *H. YOSHINO[1], K. YAMAMURO[1], Y. OGAWA[2], M. MAKINODAN[1], M. TORITSUKA[1], K. OKAMURA[1], Y. NISHIHATA[1], Y. YAMAGUCHI[1], S. KIMOTO[1], M. YAMASHITA[3], G. CORFAS[4], T. KISHIMOTO[1]
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Abstract: Juvenile social experience is crucial for the functional development of forebrain regions, especially the prefrontal cortex (PFC). We previously reported that social isolation for two weeks after weaning induces prefrontal cortex dysfunction and hypomyelination. However, the effect of social isolation on physiological properties of PFC neuronal circuit remained unknown. Since hypomyelination due to isolation is prominent in deep-layer of medial PFC (mPFC), we focused on two types of layer-5 pyramidal cells in the mPFC: prominent h-current (PH) cells and non-prominent h-current (non-PH) cells. We found that a two-week social isolation after weaning leads to a specific deterioration in action potential properties and reduction in excitatory synaptic inputs in PH cells. The effects of social isolation on PH cells, which involve reduction in functional glutamatergic synapses and AMPA/NMDA charge ratio, are specific to the two weeks after weaning and to the mPFC. We conclude that juvenile social experience plays crucial roles in the functional development in a subtype of layer-5 pyramidal cells in the mPFC. Since these neurons project to subcortical structures, a deficit in social experience during the critical period may result in immature neural circuitry between mPFC and subcortical targets.

Disclosures: H. Yoshino: None. **K. Yamamuro:** None. **Y. Ogawa:** None. **M. Makinodan:** None. **M. Toritsuka:** None. **K. Okamura:** None. **Y. Nishihata:** None. **Y. Yamaguchi:** None. **S. Kimoto:** None. **M. Yamashita:** None. **G. Corfas:** None. **T. Kishimoto:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 653.25/C37

Topic: A.07. Developmental Disorders

Support: INP Grant NC123240.1

CONACyT Grant 129303

Title: High frequency stimulation of thalamic reticular nucleus modifies aberrant oscillatory activity in a model of schizophrenia

Authors: *V. M. MAGDALENO-MADRIGAL[1], G. CONTRERAS-MURILLO[2], I. CAMACHO-ABREGO[3], J. V. NEGRETE-DÍAZ[4], A. VALDÉS-CRUZ[5], G. FLORES[6]
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Abstract: Dysfunctions of thalamo-cortical networks are implicated in schizophrenia. In the neonatal ventral hippocampal lesion (NVHL), a heuristic animal model of schizophrenia, brain oscillation changes similar to those of schizophrenic patients have been reported. The aim of this study was to analyze the effects of short-term deep brain stimulation (DBS) in the thalamic reticular nucleus on electroencephalographic (EEG) activity in the NVHL. Male and female Sprague-Dawley rats were used and the model was prepared by excitotoxicity damage of the ventral hippocampus on postnatal day 7 (PD-7). Chronic bilateral stainless steel electrodes were implanted in the TRN, thalamic dorsomedial nucleus and prelimbic area at PD-90. Rats were classified as follows: sham and NVHL groups, both groups received bilateral DBS in the TRN for 60 min (100 Hz, 100 µs pulses, 200 µA). All animals showed a sudden behavioral arrest accompanied by widespread symmetric bilateral spike-wave discharge, this activity was affected by DBS-TRN. Additionally, the power spectra of 0.5-100 Hz and the coherence of 0.5-4.5 and 35-55 Hz frequencies were modified by DBS-TRN. Our results suggest that DBS in the TRN may modify functional connectivity between different parts of the thalamo-cortical network. Additionally, our findings may suggest a beneficial effect of DBS-TRN on some preclinical aberrant oscillatory activities in a neurodevelopmental model of schizophrenia.

Disclosures: V.M. Magdaleno-Madrigal: None. **G. Contreras-Murillo:** None. **I. Camacho-Abrego:** None. **J.V. Negrete-Díaz:** None. **A. Valdés-Cruz:** None. **G. Flores:** None.

Poster

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Topic: A.07. Developmental Disorders

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Title: Abnormal craniofacial and neural development in glycosyltransferase mutant zebrafish recapitulates CDG-Ij patient phenotypes

Authors: *L. N. LUDERMAN[1,2,3], E. W. KNAPIK[5,4,2]
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Abstract: Glycosylation is an important co-translational and post-translational modification required for protein function, such as recognition by ER quality control machinery, binding, structural and metabolic activity. Due to the prevalence and necessity of glycoproteins for normal cellular function, defects within the N-glycosylation pathway result in disruptions in development and function of multiple organ systems, including the nervous, skeletomuscular, respiratory and visual systems. Mutations in over 30 genes involved in N-glycosylation of proteins have been identified as genetic causes of a group of diseases known as congenital disorders of glycosylation (CDG). CDG-Ij is caused by mutations within the *DPAGT1* gene encoding the first glycosyltransferase (GlcNAc-1-P transferase) of the N-glycosylation pathway. CDG-Ij patient symptoms include microcephaly, dysmorphic face, hypotonia, mental retardation, seizures, and exotropia. Recently, clinical studies on CDG-Ij patients have added new phenotypes to the disease spectrum to include neuromuscular phenotypes, although additional studies are needed to understand the full pathology of the disease. Prior work in our laboratory identified a mutant zebrafish line, *stumpf* (*stp*^{m365}), that carries a point mutation in a highly-conserved domain of Dpagt1. Zebrafish *stumpf* mutant phenotype includes malformed craniofacial skeleton and defects in neural tissue development, similar CDG-Ij patient phenotypes. Using both molecular and imaging techniques, the *stumpf* zebrafish mutant provides a unique vertebrate model system to study the mechanism of CDG-Ij and the disease phenotypic spectrum.

Disclosures: L.N. Luderman: None. **E.W. Knapik:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

Title: Neurosteroids abnormalities in a murine two-hit model of suicide-related behaviors in a schizophrenia-like context

Authors: *C. MAURICE-GÉLINAS[1], J. DESLAURIERS[2], O. HUBERT[1], P. SARRET[1], S. GRIGNON[1]

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Abstract: Suicide risk in patients with schizophrenia is roughly 5 times more frequent than in the general population. At odds with other clinical conditions, suicidal behaviour in schizophrenia patients does not seem to involve serotoninergic abnormalities, and its pathophysiology remains obscure. One cue to a better understanding might come from the suicide-preventing effects of clozapine, an antipsychotic with superior efficacy and specific neurochemical properties, including modulation of neurosteroid (NS) levels (e.g., allopregnanolone, a NS with known effects on GABA-mediated transmission).We recently characterized a Two-Hit murine Model of Suicide-related behaviors (SRB) in a schizophrenia-like context (THMS). In this model, pregnant C57BL/6 mice are injected with 20 mg/kg of polyinosinic/polycytidylic acid (PolyI:C) at gestational day 12 and their offspring are submitted to social isolation (SI) from postnatal days 21 to 53. In this THMS, clozapine normalized prepulse inhibition, aggressiveness, impulsivity and anxiety-like behaviours. Of note, the NS synthesis inhibitor finasteride increased aggressiveness in THMS mice and antagonized clozapine effects on locomotion, suggesting NS involvement in SRB and clozapine effects in this model.Methods: As a second step to ascertain biological explanation for these behaviors, we assessed the levels of 5-alpha-reductase (5α-reductase), $GABA_A$ subunits, translocator protein (TSPO) and cholesterol side-chain cleavage (p450scc) by qPCR or western blot (WB) analysis in animals subjected to the THMS and/or to subacute clozapine treatment. Results: qPCR analysis and WB analysis of $GABA_A$ delta subunit levels revealed no difference across conditions or treatment. Likewise, no changes in $GABA_A$ alpha4 subunits, 5α-reductase 1 and 2 levels were observed, although WB analysis of overall $GABA_A$α subunits ($GABA_A$α1-6) showed main effects of condition ($p<0.05$) and finasteride ($p<0.05$). Interestingly, gestational inflammation elicited by polyI:C inhibited the stress-induced increase in TSPO and p450scc mRNA levels. Indeed, in the prefrontal cortex and striatum, there was an increase in TSPO expression (+34% and +49%, respectively, $p<0.05$) and p450scc (+65% and +71%, respectively, $p<0.05$) in animals subjected to SI. However, in mice exposed to both conditions (prenatal polyI:C and SI), there was no elevation of TSPO levels and p450scc. Conclusion: Altogether, these results suggest that the THMS is associated with significant modifications of NS signaling. Yet, clozapine effects in this context do not seem to involve prominent changes of TSPO/p450scc levels, nor modulation of $GABA_A$ levels.

Disclosures: C. Maurice-Gélinas: None. **J. Deslauriers:** None. **O. Hubert:** None. **P. Sarret:** None. **S. Grignon:** None.

Poster

653. Neurodevelopmental Disorders: Molecular and Cellular Mechanisms II

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Topic: A.07. Developmental Disorders

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Title: The thalamus reticularis nucleus is susceptible to redox dysregulation

Authors: *P. STEULLET[1], J. CABUNGCAL[2], M. R. CUENOD[3], K. Q. DO[4]
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Abstract: Oxidative stress is a convergent mechanism affecting prefrontal parvalbumin-expressing interneurons in many animal models carrying genetic and/or environmental risks relevant to schizophrenia. Here, we examined the vulnerability to redox dysregulation of the thalamic reticularis nucleus (TRN), a region consisting of GABAergic neurons, whose vast majority express parvalbumin. Via their inhibition of thalamo-cortical neurons, TRN cells modulate thalamo-cortical communication, which is abnormal in high-risk individuals and schizophrenia patients. Recently, Berretta and colleagues found reduced parvalbumin-immunoreactive (PV-IR) cells and abnormal perineuronal nets in the TRN of schizophrenia patients. We assessed the morphological integrity and function of TRN cells in an animal model of redox dysregulation induced by low glutathione content (*Gclm* KO mice). Oxidative stress was present in TRN of KO mice, from childhood on. The oxidative stress was more prominent in TRN than in other thalamic nuclei. In all ages investigated (postnatal, days 20, 40, 90), there was reduced number of PV-IR cells in KO as compared to WT mice. Likewise, the extracellular perineuronal net surrounding PV-IR cells was altered. The firing pattern and physiological properties of TRN cells recorded in-vitro were also altered in KO mice. During spontaneous activity, less TRN cells generated bursts of action potentials in KO as compared to WT mice. The membrane potential of the TRN cells had to be more hyperpolarized in KO than in WT mice in order to produce depolarization-evoked bursts of action potentials. This indicates that TRN cells are less inclined to fire in bursting mode in KO as compared to WT mice. On the other hand, the fast-spiking tonic firing mode of TRN cells in KO was not altered. Thus, the TRN is highly vulnerable to redox dysregulation and prone to oxidative stress early during development. These data suggest that redox dysregulation could be one mechanism by which the TRN could be affected during the progression of the disease, leading to inappropriate thalamo-cortical communications and affecting for instance sleep spindles as well as selective attention.

Disclosures: P. Steullet: None. **J. Cabungcal:** None. **M.R. Cuenod:** None. **K.Q. Do:** None.

Poster

654. Development of Olfactory and Taste Circuits

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Topic: D.05. Olfaction and Taste

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Title: Unique connectivity within the necklace subsystem suggests a novel function in olfactory processing

Authors: *T. TAN, K. DRUMMEY, N. BHAGAT, W. GILLIS, J. KATON, K. MESSEMER, C. DIXON, J. NGUYEN, S. R. DATTA
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Abstract: Animals have evolved a number of anatomically and molecularly distinct olfactory subsystems to detect and appropriately respond to environmental stimuli. Canonical mammalian olfactory pathways are defined by populations of olfactory sensory neurons (OSNs) that reside within specific zones of the nasal epithelium, project to a small number of specific glomeruli in the olfactory bulb (OB), and synapse onto second-order neurons that route information to a set of higher-brain structures. The GCD “necklace” subsystem exhibits atypical anatomical organization in the periphery, with OSNs located within isolated “cul-de-sacs” of the nasal epithelium; these neurons project axons to a seemingly interconnected string of glomeruli encircling the caudal OB. However, further details about the anatomical architecture of this olfactory subsystem are absent, due in large part to the relative inaccessibility of this subsystem *in vivo* compared to other olfactory systems. To better query the organizational logic of the necklace subsystem, we developed a novel surgical preparation to expose the mouse necklace subsystem *in vivo*. Using this preparation – which provides us unprecedented access to this atypical olfactory system – we performed anatomical tracing to and from individual necklace glomeruli to identify the organizing principles by which this subsystem processes olfactory information. We observe that a single glomerulus is innervated by OSNs that are spread across multiple cul-de-sacs in the epithelium, suggesting that each glomerulus redundantly “pools” olfactory information from across the epithelium, rather than “tiling” physical olfactory space in the nose. Together with earlier results from our laboratory showing that – in stark contrast to other mammalian olfactory systems – each necklace OSN expresses multiple chemoreceptors, our results suggest that the necklace system is built to integrate diverse chemical signals,

suggesting a fundamentally distinct functional role for the necklace subsystem in mediating olfactory driven behaviors.

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Poster

654. Development of Olfactory and Taste Circuits

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Topic: D.05. Olfaction and Taste

Support: NSF CAREER 1553279

Title: A deep learning pipeline for studying olfactory bulb molecular anatomy at genomic scale

Authors: *J. B. CASTRO[1], A. ANDONIAN[2], D. PASELTINER[2]
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Abstract: The olfactory bulb (OB) receives molecularly heterogeneous and topographically organized sensory inputs. While the zonal organization of the OB's inputs is well established, we understand comparatively less about whether this organization is maintained, elaborated, or discarded in the bulb's intrinsic circuitry. To understand the bulb's genomic anatomy -- especially the possible molecular heterogeneity of its mitral cells -- we have registered thousands of in-situ-hybridization (ISH) experiments from the Allen Brain Atlas (ABA) to a set of common OB templates. Doing this at scale requires robust and automated tissue classification for groupwise registration. Here, we describe our use of convolutional neural networks to classify OB sections from the ABA in both supervised and unsupervised contexts. We observe expert-level classification of tissue sections, with accuracy approximately equal to the reproducibility of human-raters (~85% on a 6-class classification task). In preliminary analyses in which we have performed non-negative-matrix factorization based dimensionality reduction on 1,000 registered data sets, we find that gene expression in the mitral cell layer is well-described by 3 non-overlapping spatial modes that explain >90% of expression variance. Intriguingly, two of these modes strongly resemble the dorsal and ventral domains of the bulb defined by OCAM labeled inputs, suggesting that the topographic specialization of bulbar inputs may also be evident in second-order olfactory system neurons.

Disclosures: **J.B. Castro:** None. **A. Andonian:** None. **D. Paseltiner:** None.

Poster

654. Development of Olfactory and Taste Circuits

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Topic: D.05. Olfaction and Taste

Support: Department of Neuroscience Start-up funds

Title: Loss of cilia on granule cells alters olfactory bulb morphology

Authors: *J. MCINTYRE, A. K. PARKER
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Abstract: Olfactory sensory neurons (OSNs) project axons into the olfactory bulb (OB), where they form synapses with mitral cell dendrites in glomeruli. The activation pattern of glomeruli, and associated mitral cells underlie odor coding in the OB. Within this network are interneurons that shape synaptic input from OSNs as well as activity of mitral cells. Glomerular activity also depends on innervation from higher brain regions that supply modulation to the synaptic circuits. For example, neurons in the OB can be modulated by neural hormones associated with hunger and satiety. An unexplored mechanism of neural modulation involves primary cilia, evolutionarily conserved organelles, the function as signaling centers for numerous extracellular cues and several neuromodulatory G-protein coupled receptors (GPCRs) are localized to neuronal primary cilia. The role of neuronal cilia, and the GPCRs enriched in them, however remains unclear. Recent data suggests neuronal cilia regulate dendritic growth and branching patterns as well as agonist induced activity. The goal of this study is to identify neuromodulatory GPCRs within cilia of neurons in the OB and to determine a role for these organelles. Using in situ hybridization and immunohistochemistry we have identified the expression and localization of several neuromodulatory GPCRs in distinct OB neuronal populations. mRNAs for several GPCRs including GPR161, somatostatin receptor type 3 (SSTR3), and melanin-concentrating hormone receptor (MCHR1) were expressed in neurons in the OB. IHC for SSTR3 revealed localization to cilia on mitral cells and granule cells but absent from periglomerular interneurons. In contrast MCHR1 localized to a subset of periglomerular interneurons and granule cells but not mitral cells. Granule cells typically only expressed either SSTR3 or MCHR1, but in a subset of cells they were co-localized. The localization of SSTR3 and MCHR1 to largely interneurons suggests a role for their regulation of granules cells in response to neuromodulators in order to shape olfactory processing. To investigate a potential function of cilia on mature granule neurons, we used Gad2^{ires}Cre mice to selective knockout of the ciliary gene *Ift88*. Loss of *Ift88* resulted in widespread loss of cilia on granule cells. While at 3 weeks of age no morphological changes were seen, at 6 weeks of age, the OB of knockout mice was noticeably disorganized and the glomeruli were significantly smaller. Additionally, innervation by OSN axons and

dopaminergic neurons was decreased. These results indicate that cilia on mature interneurons are important for their function and the maintenance of the OB.

Disclosures: J. McIntyre: None. **A.K. Parker:** None.

Poster

654. Development of Olfactory and Taste Circuits

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Program#/Poster#: 654.04/C44

Topic: D.05. Olfaction and Taste

Title: Spatial and functional connectivity of perinatal and adult-born granule cells in the mouse olfactory bulb

Authors: *M. PALLOTTO, K. L. BRIGGMAN
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Abstract: Granule cells (GCs) are the main GABAergic interneurons of the olfactory bulb (OB). They are produced from birth to adulthood and inhibit the activity of mitral and tufted cells (M/TCs), with whom they make dendro-dendritic synapse. MCs and TCs are functionally distinct cell types and process different aspects of olfactory information, forming two different sub-circuits. The role of GCs in the OB has been extensively investigated. However, whether the time of birth of these interneurons contributes differently to the inhibition of MC and TC output neurons is unknown.
The aim of this work is to investigate, in adult mice, the functional connectivity of GCs with MCs and TCs as a function of the time of birth of GCs and their developmental stage.
We use Pdch::CRE transgenic mice, in which injections of a light activated ion channel, fl-ChETA AAV, allow expression specifically in M/TCs. In OB slices, whole field light stimulation elicits axon potentials in MCs. Using a micro-mirror device (DMD), we are able to selectively light-activate specific M or TCs with high temporal and spatial resolution. In the same mouse, we inject a combination of AAV vectors encoding calcium indicators (GECIs: GCaMP6s or Ruby-GCaMP6s) at postnatal day 2 (p2) or p30 to label and identify perinatal GCs and both immature and mature adult-born GCs. Preliminary data show that both perinatal and adult-born GCs respond to a variety of light stimuli including specific combinations of M and TCs. We are in the process of mapping the spatial distribution of responsive GC cell bodies relative to the distance from the stimulus location (M or T cell bodies).
Lastly, to validate these data we are collecting a 3D volume using serial block-face EM of a mouse injected with AAV of three different colors (GFP, RFP or cerulean) at different time points (p2, p30 and p50). Altogether, these experiments will help us to investigate the specificity of functional connectivity between MCs, TCs and adult-born and perinatal born GCs, and help us to understand better the connectivity among OB neurons and the role of adult generated neurons.

Disclosures: **M. Pallotto:** None. **K.L. Briggman:** None.

Poster

654. Development of Olfactory and Taste Circuits

Location: Halls A-C

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Topic: D.05. Olfaction and Taste

Title: Plastic changes in the pre-synaptic landscape of mitral\tufted cells following parturition

Authors: *A. VINOGRAD[1,2], G.-I. TASAKA[1,2], L. KREINES[1,2], A. MIZRAHI[1,2]
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Abstract: Motherhood is accompanied by new behaviors aimed at ensuring the survival and wellbeing of the offspring. Newly appearing maternal behaviors are most likely associated with alterations in neuronal circuits that would in turn affect odor coding. The olfactory bulb (OB), the first central processing center in olfaction, serves as an essential computational hub for odor coding. We recently discovered that motherhood was accompanied by an increased inhibitory drive onto Mitral\Tufted (M/T) cells - the projection neurons of the OB. To study circuit motifs associated with this increased inhibition, we studied the presynaptic connectivity landscapes of M/T cells in naïve mice and mothers using monosynaptic rabies trans synaptic tracing. We targeted M/T cells by using a cre-dependent version of rabies virus injected into the tbet-cre mouse line. Rabies tracing revealed both local as well as long range synaptic inputs on M/T cells, which was then quantified in naïve mice and mothers. While local pre-synaptic landscapes of M/T cells in mothers were stable, several long-range landscapes were dramatically plastic. Specifically, the number of inputs per M/T cells from the piriform cortex (PCx) increased two-fold. These data suggest that feedback connections into the OB have a central role in re-shaping M/T responses following motherhood and signifies the PCx-to-M/T as a central circuit motif for parental plasticity.

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Poster

654. Development of Olfactory and Taste Circuits

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Support: NIH F30 DE023479

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NIH R01 DC014428

Title: Biphasic functions for the GDNF-Ret signaling pathway in chemosensory neuron development and diversification

Authors: *C. R. DONNELLY[1], A. SHAH[2], C. MISTRETTA[2], R. M. BRADLEY[2], B. A. PIERCHALA[2]
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Abstract: The development of the taste system relies on the coordinated regulation of cues that direct the simultaneous development of both peripheral taste organs and innervating sensory ganglia. However, the underlying mechanisms remain poorly understood. In this study, we describe a novel, biphasic function for the glial cell line-derived neurotrophic factor (GDNF) in the development and subsequent diversification of chemosensory neurons within the geniculate ganglion (GG). GDNF, acting through the receptor tyrosine kinase, Ret, regulates the expression of the chemosensory fate determinant Phox2b early in GG development. *Ret*$^{-/-}$ mice, but not *Ret*$^{fx/fx}$; *Phox2b*-Cre mice, display a profound loss of Phox2b expression with subsequent chemosensory innervation deficits, indicating Ret is required for initiation of Phox2b, but not its maintenance. Ret expression is extinguished perinatally, but re-emerges postnatally in a subpopulation of large-diameter GFRα1+ GG neurons expressing the mechanoreceptor marker NF200. Intriguingly, we observed that ablation of these neurons in adult *Ret*-Cre/ER^{T2}; *Rosa26*$^{LSL\text{-}DTA}$ mice caused a specific loss of tactile but not chemical or thermal electrophysiological responses. Overall, the GDNF-Ret pathway exerts two critical and distinct functions in the peripheral taste system: embryonic chemosensory cell fate determination and the specification of lingual mechanoreceptors.

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Poster

654. Development of Olfactory and Taste Circuits

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NIH Grant R03 DC013988

FSU Neuroscience Fellowship

Title: Regulation of deep short axon cells (dSACs) in the olfactory bulb as part of a microcircuit involving the gut hormone, glucagon-like peptide-1 (GLP-1)

Authors: *Z. HUANG[1], N. THIEBAUD[2], D. A. FADOOL[3]
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Abstract: Glucagon-like peptide-1 (GLP-1) and its analogues are promising drug candidates for treating type 2 *diabetes mellitus* given their important role in peripheral glucose metabolism. The recent development of a transgenic reporter for preproglucagon allowed us to previously identify GLP-1 in deep short axon cells (dSACs) and the expression of GLP-1 receptor in downstream mitral cells (MCs) of the olfactory bulb (OB). GLP-1 modulation of MCs was dependent upon potassium channel Kv1.3. While optogenetic analysis of this circuit has been performed, endogenous activation of the dSACs circuit is unknown. Herein, we used an *in vitro*, brain slice approach to investigate the GLP-1 dSACs activation. Juvenile mice (P20 to P45) of both sexes were used to examine the involvement of centrifugal projections from higher brain areas including serotonergic, cholinergic, and noradrenergic afferents. Bath application of serotonin (40 µM, n = 4) and norepinephrine (100 µM, n = 4) had no effect on the evoked firing frequency. Acetylcholine (ACh; 100 µM), however, led to either inhibition or excitation of GLP-1 dSACs. For inhibition, ACh induced a small outward current (5.1 ± 1.8 pA, n = 9) recorded by voltage-clamp when dSACs were held at −70 mV. When injecting a small current in current-clamp mode, ACh delayed the latency to first spike (control: 253 ± 30 ms, ACh: 396 ± 4 ms; n = 2). For excitation, bath application of ACh resulted in 2.1 ± 0.6-fold increase in firing frequency (n = 19). Previous evidence has shown that GLP-1 neurons in the NTS can be modulated by metabolic-related hormones such as leptin and cholecystokinin (CCK). We found that GLP-1 dSACs could be modulated by CCK, but not by leptin. Bath application of CCK (0.8 µM) led to either cessation of firing (n = 7) or an increase in firing of 1.8 ± 0.3-fold (n = 10). When we switched the bath glucose concentration from 22 mM to 1 mM, a subset of GLP-1 dSACs (6 of 16 tested cells) demonstrated a 1.2 ± 0.4-fold increase in firing frequency that was accompanied by a 1-2 mV depolarization. Lastly, mice were injected intraperitoneally (200 nmol/kg) with the GLP-1 analogue exendin-4 or control saline and tested 30 minutes post injection in a habituation-dishabituation odor test. Mice receiving exendin-4 failed to significantly dishabituate, demonstrating impaired ability to discriminate the odor ethyl octanoate from ethyl hexanoate (control: 2.2 ± 1.2 new/old odor explore time ratio, n = 11; exendin-4: 0.7 ± 0.5 ratio, n = 7). Our data support that GLP-1 dSACs are differentially modulated by the neurotransmitter ACh and the metabolic hormone CCK. Some GLP-1 dSACs are glucose sensitive and *in vivo* application of GLP-1 analogue dampens the discrimination of odors.

Disclosures: Z. Huang: None. **N. Thiebaud:** None. **D.A. Fadool:** None.

Poster

654. Development of Olfactory and Taste Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 654.08/C48

Topic: D.05. Olfaction and Taste

Support: NIH Grant DC015137

Title: Spine fluctuations and adult neurogenesis jointly rewire the olfactory network and reshape sensory processing

Authors: *H. RIECKE, J. H. MENG, J. PARK
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Abstract: The mammalian olfactory system exhibits profound structural plasticity. While large numbers of new granule cells enter the olfactory bulb even in adult animals and form reciprocal synapses with the mitral cells, the spines of the reciprocal synapses of young and old granule cells exhibit highly dynamic turnover. In addition, the granule cells are the targets of extensive centrifugal projections that originate in part in cortical areas. What do these mechanisms contribute to olfactory processing? How do they complement each other? We address these questions using computational modeling.
In recent work on spine fluctuations we have shown that the experimentally observed age-dependence of spine stability can arise from a Hebbian mechanism that stabilizes synapses connecting strongly active cells. Through the resulting restructuring the bulbar network learns to enhance differences between very similar odors [1].
Here we first show that adult neurogenesis alone is sufficient to restructure the bulbar network such that after learning most mitral cells are significantly more strongly adapted to the learned, familiar odor than to a novel odor, as has been observed experimentally [2]. Upon familiarizing the bulbar network with a pair of very similar odors the differences between the bulbar representations of these odors are enhanced, while learning a pair of dissimilar odors reduces their differences, in qualitative agreement with recent experiments [3]. This difference in network evolution also manifests itself in the number of model mitral cells whose odor responses contribute to the differentiation of the odors compared to those that do not [3].
We then investigate a model that combines spine fluctuations and adult neurogenesis, addressing how each contributes to the speed of adaptation and to the network's ability to adapt to completely novel odors. The apical synapses between granule and mitral cells develop much later than the proximal synapses that receive centrifugal inputs. We investigate to what extent this enhances the odor-specificity of the network structure and its odor processing.
[1] K. Sailor et al., Neuron 91 (2016) 384.

[2] H.K. Kato, M.W. Chu, J.S. Isaacson, T. Komiyama, Neuron 76 (2012) 962.
[3] M.W. Chu, W.L. Li, T. Komiyama, Neuron 92 (2016) 174.

Disclosures: **H. Riecke:** None. **J.H. Meng:** None. **J. Park:** None.

Poster

654. Development of Olfactory and Taste Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 654.09/DP05/C49 (Dynamic Poster)

Topic: D.05. Olfaction and Taste

Title: Investigating the subtype-specific connectivity of periglomerular cells in the mouse olfactory bulb using correlative serial block-face electron microscopy

Authors: *K. FULTON[1,2], K. L. BRIGGMAN[1]
[1]Neurosci., NIH, Bethesda, MD; [2]Neurosci., Brown Univ., Providence, RI

Abstract: A dense reconstruction of synaptic connectivity requires high-resolution 3D electron microscopy (EM) data. However, EM data alone typically lacks functional information about the neurons in the data. One way to add functional information to an EM dataset is to fluorescently immuno-label tissue for specific functionally relevant proteins and to optically image the distribution of proteins prior to preparing the tissue for EM. Unfortunately, current immunohistochemistry protocols rely on detergent permeabilization, which significantly compromises tissue ultrastructure and renders such protocols incompatible with high quality EM. We recently showed that preservation of extracellular space (ECS) improves access for antibodies with minimal detergent permeabilization (Pallotto and Watkins et al., 2015). We have utilized the ECS preservation in acutely fixed sections and developed a permeabilization-free immunolabeling protocol compatible with serial block-face scanning electron microscopy (SBEM), which permits deep antibody penetration and preserves ultrastructure integrity. SBEM, in combination with immunofluorescent labeling of neuron subtypes in the same piece of tissue, allows us to correlate the morphological and physiological properties of neurons through a dense reconstruction of the synaptic connectivity.
We are utilizing this approach to investigate the differences in synaptic connectivity between neurochemically-distinct periglomerular cell (PGC) subtypes and olfactory bulb (OB) principle neurons, mitral (MCs) and tufted cells (TCs), to understand if PGC subtypes have functionally distinct roles in odor processing. Recent work demonstrated that PGCs differentially modulate the spatiotemporal dynamics of MCs and TCs, which results in antiphase coupling of the MCs and TCs relative to the sniff cycle. Specific connectivity between principle neurons and PGC subtypes would imply heterogeneity in the roles of PGC subtypes modulating olfactory information. However, due to the complexity of the circuit, it has been difficult to study the functional connectivity using standard recording methods. As a result, the functional roles of the

PGC subtypes remain unknown due to a lack of knowledge about how they connect to MCs and TCs. Understanding the connectivity of PGC subtypes with MCs and TCs will be important for future investigations into the subtype-specific involvement in regulating mitral versus tufted cell activity in the OB. Finally, this experiment will challenge the canonical view of olfactory bulb circuitry by potentially revealing previously unidentified wiring specificity underlying OB computations.

Disclosures: K. Fulton: None. **K.L. Briggman:** None.

Poster

654. Development of Olfactory and Taste Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 654.10/C50

Topic: D.05. Olfaction and Taste

Support: MOST

Title: Communication between two brain hemispheres: The wiring of bilateral local interneurons in *Drosophila* olfactory system

Authors: *S.-H. LIN, H.-J. LIN, H.-H. CHANG, K.-T. TSAI, Y.-H. CHOU
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Abstract: How two brain hemispheres communicate to each other and to what extent is largely unknown. Understanding how neurons wire to connect two brain hemispheres is essential to know how information is communicated between them. Olfactory local interneurons(LNs) provide horizontal connections inside the antennal lobe(AL), the first olfactory processing center in *Drosophila* olfactory system, and are essential for neural computation and information processing. Our previously work demonstrated that there are unilateral LNs with process restricted in one AL and bilateral LNs that innervate both ALs. Compared to unilateral LNs, the properties of bilateral LNs are largely unknown. Here we characterize bilateral LNs at single-cell resolution by Mosaic Analysis with a Repressible Cell Marker (MARCM), and simultaneously explored their neurotransmitter identities and birth timing. We systematically analyzed all bilateral LNs born in sixteen consecutive twelve-hour time windows covering larval and pupal development and obtained >1078 single cell clones. We found these bilateral LNs have either roughly symmetric or asymmetric innervation patterns in the ipsilateral and contralateral AL. Their morphologies are also highly diverse and likely with certain degree of variability. We are scoring individual bilateral LNs' arborization patterns, and analyzing their synapse distributions and neurotransmitters profiles. Our work will allow us to address whether there is any correlations between bilateral LNs' innervation pattern, neurotransmitters, and /or birth timing.

We will then focus on several types of bilateral LNs to investigate their development and potential biological functions.

Disclosures: S. Lin: None. **H. Lin:** None. **H. Chang:** None. **K. Tsai:** None. **Y. Chou:** None.

Poster

654. Development of Olfactory and Taste Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 654.11/C51

Topic: D.05. Olfaction and Taste

Support: NIH R03 DC013997-01

Grant-In-Aid of Research from Sigma Xi, The Scientific Research Society

Title: Serotonergic modulation differentially targets distinct network elements within the antennal lobe of *Drosophila melanogaster*

Authors: *T. R. SIZEMORE, A. M. DACKS
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Abstract: Neuromodulation confers flexibility to anatomically-restricted neural networks so that animals can properly respond to complex internal and external demands. However, determining the mechanisms underlying neuromodulation is challenging without knowledge of the functional class and spatial organization of neurons that express individual neuromodulatory receptors. Here, we describe the number and functional identities of neurons in the antennal lobe of *Drosophila melanogaster* that express each of the receptors for one such neuromodulator, serotonin (5-HT). Although 5-HT enhances odor-evoked responses of antennal lobe projection neurons (PNs) and local interneurons (LNs), the receptor basis for this enhancement is unknown. We used endogenous reporters of transcription and translation for each of the five 5-HT receptors (5-HTRs) to identify neurons, based on cell class and transmitter content, that express each receptor. We find that specific receptor types are expressed by distinct combinations of functional neuronal classes. For instance, the excitatory PNs express the excitatory 5-HTRs, while distinct classes of LNs each express different 5-HTRs. This study therefore provides a detailed atlas of 5-HT receptor expression within a well-characterized neural network, and enables future dissection of the role of serotonergic modulation of olfactory processing.

Disclosures: T.R. Sizemore: None. **A.M. Dacks:** None.

Poster

654. Development of Olfactory and Taste Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 654.12/C52

Topic: D.05. Olfaction and Taste

Support: NIH grant R03 DC013997-01

USAFOSR FA9550-17- 1-0117

Title: Keystone relationships of transmitter co-expression predict patterns of local interneuron heterogeneity

Authors: *K. M. LIZBINSKI[1], G. F. MARSAT[1], A. M. DACKS[2]
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Abstract: Heterogeneity in individual neural properties provides a network with multiple coding strategies resulting in greater resolution for information processing. However, the organizing principles that support heterogeneity within a neural class are often poorly understood. Here, we focus on a highly heterogeneous population of local interneurons whose traits co-vary seemingly at random. We systematically determine the co-expression of neuropeptides and GABA by local interneurons (LNs) in the olfactory system of the moth, *Manduca sexta* and find that the high degree of neuropeptide co-expression appears random on a neuron by neuron basis. Using a computational model, we demonstrate that neuropeptides are co-expressed in a specific, non-random pattern, and that deterministic, keystone relationships explain the overall heterogeneity of transmitter co-expression. Olfactory receptor neurons, LNs and projection neurons all expressed four of five neuropeptide receptors and the $GABA_B$ receptor, suggesting that LN activation influences multiple stages in olfactory processing. Tachykinin exhibited “all-or-none” co-expression with other neuropeptides and the tachykinin receptor was not expressed by LNs, suggesting that tachykinergic LNs are functionally distinct from other LN types. Our data demonstrates that the role of LN subtypes are finely tuned by the expression of specific subsets of neuropeptides and that the influence of peptidergic signaling by LNs likely influences multiple stages of olfactory processing.

Disclosures: K.M. Lizbinski: None. **G.F. Marsat:** None. **A.M. Dacks:** None.

Poster

654. Development of Olfactory and Taste Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 654.13/C53

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Internal support from LUC

Title: Ephrin-A/EphA signaling guides embryonic gustatory and somatosensory lingual afferents

Authors: K. DOSHI[1], N. HOSHINO[1], J. HWANG[1], R. W. TREFFY[2], *M. W. ROCHLIN[1]
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Abstract: Ephs and ephrins are cell surface molecules that act as ligands and receptors for one another, initiating signaling cascades that can cause repulsion, arborization, or growth promotion of axons. They are known to have important roles in axon pathfinding and targeting throughout the nervous system, but little is known of their roles in the innervation of gustatory papillae. There are two classes of Ephs and ephrins: ephrin-As are lipid-linked proteins that interact predominantly with EphAs, whereas ephrin-Bs are transmembrane proteins that interact predominantly with EphBs. At the time that gustatory axons are penetrating fungiform papilla epithelium in rats and mice, anti-ephrin-A3 and anti-ephrin-A1 label the lingual epithelium broadly, but the labeling is less intense in gustatory epithelium, particularly the area traversed by gustatory axons. In situ hybridization results support these findings. Anti-EphA5 and -EphA7 label afferents within nascent fungiform papillae. Using stripe assays, we show that ephrin-A-Fc and EphA-Fc fusion proteins repel geniculate (gustatory) and trigeminal (somatosensory) ganglion neurites dose dependently in vitro. Together, these data are consistent with a guidance role for ephrin-As and potentially EphAs during pathfinding and targeting of gustatory and somatosensory axons in the tongue. Intriguingly, ephrin-A3 repels E18 rat-derived geniculate neurites with significantly greater potency than trigeminal neurites. This raises the possibility that ephrin-A signaling corrals gustatory afferents into the center of fungiform papilla epithelium, where the taste bud will form, and segregates them from the less ephrin-A-sensitive somatosensory afferents that supply the surrounding papilla epithelium. Ephrin-B2 is also expressed along the dorsal lingual epithelium, albeit later than ephrin-A1 and -A3, after axons penetrate the epithelium; and ephrin-B-Fcs are repellent in vitro. Combining intermediate concentrations of ephrin-A-Fcs and ephrin-B-Fcs in the same stripe results in additive repellent effects. Preliminary results from triple knockout mice lacking ephrin-A1, -A3 and -A4 suggest that normal innervation depends on ephrin-A signaling.

Disclosures: K. Doshi: None. **N. Hoshino:** None. **J. Hwang:** None. **R.W. Treffy:** None. **M.W. Rochlin:** None.

Poster

654. Development of Olfactory and Taste Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 654.14/C54

Topic: D.05. Olfaction and Taste

Support: NIH Grant DC04846

Office of Research and Creative Activity, University of Nebraska at Omaha

Title: Cell loss in the rat geniculate ganglion following neonatal chorda tympani transection

Authors: *L. J. MARTIN[1], K. K. SAMSON[2], S. I. SOLLARS[1]
[1]Univ. of Nebraska At Omaha, Omaha, NE; [2]Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Outcomes following injury often differ drastically depending on the age during insult. The rat chorda tympani (CT) taste nerve regenerates following transection, unless denervation occurs at or prior to postnatal day ten (P10). We recently found that this lack of regeneration is associated with a dramatic loss of CT terminal field volume in the brainstem 50 days after injury, suggesting that early transection causes CT cell loss. To determine whether cell death can explain the decrease in terminal field after early CT injury, we counted cells in the geniculate ganglion 50 days following CT transection in neonatal (P5) or adult (P50) rats. Adult rats undergoing CT transection were used as controls since there is little to no CT cell or terminal field loss in these animals (Reddaway et al., *J. Comp. Neurol.* 2012, *520* (11), 2395-2413) and transection allows the application of a neural tracer. Female neonatal or adult Sprague-Dawley rats were anesthetized with Brevital, and the CT was assessed through an incision in the neck before being cut. To differentiate CT cells from other geniculate ganglion sensory cells, the nerve was labeled with the long-lasting tracer DiI. After cutting the CT, crystals of DiI (1,1'-Dioctadecyl-3,3,3',3'-Tetramethylindocarbocyanine Perchlorate) or a DiI paste was placed on the cut portion of the nerve. Fifty days after the nerve transection and label, rats were perfused and a portion of the facial nerve was extracted with the geniculate ganglion and greater superficial petrosal nerve attached. Tissue was cut into 10 μm sections using a cryostat. An epifluorescent microscope was used to identify DiI-labeled CT cell bodies in the geniculate ganglion which were traced using Neurolucida (MBF Bioscience). Tissue was stained with cresyl violet, and the total number of ganglion cells was determined by counting cells with a visible nucleolus. Results show that there are significantly fewer ganglion cells in rats that received CT transection at P5 compared to P50 ($t(4) = 3.232$, $p < .05$). On average, there were 278 fewer ganglion cells in the early cut animals, indicating that a large portion of CT cells die following early CTX. This finding suggests that the substantial loss of CT terminal field after early denervation is caused by CT cell death. Additionally, the maintenance of many, but not all, CT cells appears to be dependent on nerve integrity during postnatal development. We are currently assessing the

number of DiI-labeled cells to determine whether ganglion cell loss is limited to chorda tympani cells, or if adjacent gustatory or somatosensory cells are impacted as well.

Disclosures: L.J. Martin: None. **K.K. Samson:** None. **S.I. Sollars:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.01/C55

Topic: D.05. Olfaction and Taste

Support: Telethon GGP11116A

Title: Altered migration of inhibitory interneurons in a mouse model of intellectual disability

Authors: A. MASET[1], L. GALLA[2,1], *C. LODOVICHI[2,1,3]
[1]Venetian Inst. of Mol. Med., Venetian Inst. of Mol. Med., Padova, Italy; [2]Neurosci. Inst. CNR, Neurosci. Inst. CNR - Fondazione, Padova, Italy; [3]Armenise Harvard CDA, Padova, Italy

Abstract: Oligophrenin1 (OPHN1), a X-linked gene associated to intellectual disability, encodes a Rho-GTPase activating protein that is thought to regulate several developmental processes including axon outgrowth, dendritic maturation and cell migration. How OPHN1 could affect circuit formation and function leading to cognitive dysfunction remain obscure. Neuronal migration is one of the fundamental process that underlies proper assembly and function of neuronal circuits. Migration occurs mostly during embryonic life although it persists in the sub-ventricular zone (SVZ), in adulthood. Neuronal precursors generated in the SVZ, migrate along the rostral migratory stream (RMS) to reach the olfactory bulb (OB), where they become mature interneurons. To understand the impact of OPHN1 on cell migration, we employed a line of mice expressing a null mutation of OPHN1. By combining birthdating experiments and lentiviral vectors to labels progenitors in the SVZ, we found that the progression, the morphology and the directionality of migrating cells is deeply perturbed in OPHN1 ko mice. To investigate the mechanism underlying altered cell migration, we performed time-lapse of migrating neuroblasts, *in vivo*, testing compounds that have been shown to modulate cell migration, such as GABA. GABA is abundantly present in the rostral migratory stream. It is produced by migrating neuroblasts and is known to modulate rate of migration acting on neuronal precursor in a paracrine-autocrine manner. We found that the response to GABA of migrating neuroblasts was deeply altered in OPHN1 KO mice.

Disclosures: A. Maset: None. **L. Galla:** None. **C. Lodovichi:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.02/C56

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NICHD Intramural Grant

Title: Interneuron migration and synaptic integration in Lis1 mutant mice

Authors: *T. G. EKINS[1,2], J. A. D'AMOUR[1], C. J. MCBAIN[1]
[1]NIH/NICHD, Bethesda, MD; [2]Brown Univ., Providence, RI

Abstract: Classical lissencephaly is a neuronal migration disorder caused by PAFAH1B1 (Lis1) haploinsufficiency and is characterized by developmental delays, agyria, mislamination of brain structures and epilepsy. In the current study we investigate the consequences of lis1 haploinsufficiency at the cell and circuit level. To this end, we have utilized lis1 heterozygous (lis1+/-) and a lis1 conditional knock-out mouse lines (Lis1fl/+). The latter was crossed to several cre lines to conditionally delete one copy of lis1 selectively in pyramidal cells (Emx1-Cre), all interneurons (INTs; Dlx5/6-Cre) or a subset of INTs that are derived from the medial ganglionic eminence (Nkx2.1-Cre). Emx1-Cre heterozygous deletion of lis1 resulted in heterotopic banding similar to the lis1+/- mouse, while Nkx2.1-cre heterozygous deletion did not result in heterotopic banding. We observed that by late adolescence, the same number of parvalbumin+ interneurons, somatostatin+ INTs, and reelin+ INTs are present in CA1 for all of the previously listed genetic lines. However, within CA1, these INT populations were shifted to more superficial regions away from stratum oriens and towards stratum radiatum across. These results suggest that INTs reach the hippocampus in normal numbers but are mislocated along the radial axis, suggesting that the second phase of INT migration (radial migration) is disrupted in lis1 mutant mice. Interestingly, this is true for lines where only PCs lack lis1, and where only INTs lack lis1, suggesting that both expression of lis1 in INTs and PC somatic position are necessary for proper migration of interneurons. To further study this phenomenon, we will use a tamoxifen inducible Nkx2.1-cre line crossed to Lis1fl/+ mice at various embryonic time points (e12-e17) to closely follow the tangential and radial migration of small groups of INTs into the hippocampus. Subsequently we will isolate the time point where the most radial migration of INTs occurs and image this migration in real-time using live slices from embryonic mice. In addition, to investigate how migration deficits may affect hippocampal connectivity we will perform electrophysiological analyses in lis1 mice to assess the intrinsic physiology, functional properties and synaptic integration of INTs within hippocampal networks. We anticipate that our study will reveal the circuit deficits relating to INT function that may underlie the increased propensity for epileptic episodes that is described in lissencephaly.

Disclosures: **T.G. Ekins:** None. **J.A. D'Amour:** None. **C.J. McBain:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.03/C57

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Title: A role for Med12 and Wnt signaling in regulation of oxytocin expression

Authors: *E. D. SPIKOL, E. GLASGOW
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Abstract: The neuroendocrine system controls homeostasis, metabolism, mood and sexual behaviors. Disruptions in its development and regulation are associated with congenital abnormalities and neuropsychiatric disorders, necessitating a more thorough understanding of molecular control of neuroendocrine cell populations. Reduced oxytocin is a feature of Prader-Willi syndrome, a neurobehavioral disorder characterized by dysregulated social behavior and insatiable appetite. Here, we find that oxytocin expression is eliminated in med12 mutant embryos, while upstream regulators remain intact. Med12 is a regulatory component of the Mediator complex, which facilitates interaction between gene-specific transcription factors and general transcription machinery. Since Med12 was shown to transduce Wnt-signaling, and Wnt-signaling is known to influence patterning of the hypothalamus, we hypothesized that disruption of Wnt-signaling was responsible for lost oxytocin expression in med12 mutants. Indeed, we found that Med12 is largely epistatic to Wnt-signaling, thus confirming a role for Med12 in Wnt-signaling during zebrafish development. However, we also found that oxytocin expression was reduced in apc mutants, which have overactive Wnt-signaling, and unchanged in embryos treated with Wnt inhibitors. These surprising results indicate that the role of Med12 in oxytocin expression is independent of Wnt-signaling. Additionally, suppression of Wnt-signaling appears to be required for oxytocin expression. Using a chemical Wnt activator, we found that sensitivity of oxytocin cells to overactive Wnt signaling aligns with the earliest recorded oxytocin expression, around 30 hours post-fertilization. We hypothesize that a transient Wnt-repressive center is required for oxytocin cell and hypothalamic development. A more complete understanding of the molecular control of oxytocin expression is especially relevant given the increasing appreciation for the role of oxytocin in social behavior and mental health.

Disclosures: **E.D. Spikol:** None. **E. Glasgow:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.04/C58

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Title: Effects of prenatal alcohol exposure in rats on corticotropin-releasing factor type 1 receptor expression throughout the limbic system and hypothalamus

Authors: *S. BOUQUIN[1], C. R. OLGUIN[1], J. WAGNER[2], D. D. SAVAGE II[3], N. PENTKOWSKI[2]
[1]Psychology, [2]Univ. of New Mexico, Albuquerque, NM; [3]Neurosciences, Univ. of New Mexico Sch. of Med., Albuquerque, NM

Abstract: Prenatal alcohol exposure (PAE) detrimentally affects the development of numerous biological systems. Previous work indicates that animals with a history of PAE exhibit normal basal corticosterone levels, yet are stress hyper responsive, which may result from alterations in the corticotropin-releasing factor (CRF) signaling system. CRF controls the hypothalamic-pituitary-adrenal (HPA) axis response to stress via actions at two G protein-coupled receptors, termed CRF_1 and CRF_2. Chronic stress over activates the HPA axis, which in turn, increases CRF production and increased expression of CRF_1. Previous studies using CRF knockout mice indicate differential involvement of CRF_1 and CRF_2 in mediating stress. After exposure to chronic stress, CRF_1 knockout and double knockout mice were resistant to the negative effects of stress, while CRF_2 knockout mice exhibited heightened anxiety and sensitivity to stress. It has been proposed that CRF_1 and CRF_2 work in conjunction as a negative feedback loop, with CRF_1 acting as the excitatory mechanism and CRF_2 acting as the inhibitory mechanism. While evidence indicates that PAE increases both HPA responsivity and CRF levels, it is still unclear whether or how PAE affects basal CRF receptor expression. This study examined the effects of PAE on CRF_1 expression in key brain regions related to cognition and stress responsivity (hippocampus, hypothalamus, prefrontal cortex and amygdala). Adult Long-Evans rats (n=29) from either PAE litter dams (n=14) or saccharin litter dams (n=15) were perfused with 4% paraformaldehyde, and the brains were removed, cryoprotected, sectioned and processed for CRF_1 expression. Overall, no statistically significant differences in CRF_1 levels were observed between PAE and control animals. In the prefrontal cortex and hypothalamus, both control and PAE males had higher CRF_1 levels compared to females. However, in the hippocampus, both control and PAE females had higher CRF_1 levels compared to males. These results indicate sex differences in brain regions affected by PAE.

Disclosures: S. Bouquin: None. **C.R. Olguin:** None. **J. Wagner:** None. **D.D. Savage II:** None. **N. Pentkowski:** None.

Poster

655. Limbic System Development

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Program#/Poster#: 655.05/C59

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Intramural Research Programs of the National Institute of Diabetes and Digestive and Kidney Diseases (DK043304-23)

Title: Hippocampal dentate gyrus impairments in Gnb5 heterozygous mice

Authors: *A. AWE, J. ZHANG, M. PANDEY, P. ADIKARAM, W. F. SIMONDS
Natl. Inst. of Diabetes and Digestive and Kidney Dis., NIH, Bethesda, MD

Abstract: Gβ5 is a structurally divergent isoform of the Gβ protein family that is encoded by *Gnb5*. Gβ5 in combination with the R7 subfamily of regulator of G-protein signaling (R7-RGS) proteins and the R7-RGS binding protein regulate G-protein coupled receptor signaling in the brain by accelerating inactivation of $G\alpha_{i/o}$ subunits. Homozygous knockout of *Gnb5* in mice results in alterations in motor learning capacity and structural abnormalities in the brain, including in the hippocampal dentate gyrus (DG), a structure essential to memory formation and spatial navigation. Furthermore, homozygous loss of function mutations in *GNB5* in humans results in a recently-described cognitive disability and unique neuropsychiatric phenotype characterized by motor and speech delays, and attention deficits. However, although roughly 2% of the human population is heterozygous for damaging *GNB5* mutations, little is known about potential impairments in mice or humans heterozygous for *Gnb5* loss of function mutations. This study investigates possible hippocampal DG impairments in $Gnb5^{+/-}$ mice and any associated functional consequences. Employing cresyl violet and immunohistochemistry staining techniques, we investigated possible alterations to the structural organization of the DG and perturbations in cell composition of the DG hilus. We show that $Gnb5^{+/-}$ mice develop lateralized abnormalities of left versus right DG hilus area that were not observed in *Gnb5* wild-type mice. Further, we observe a more pronounced abnormality in left hilus area than the right hilus. We find that $Gnb5^{+/-}$ mice also display perturbations in DG hilus cell composition affecting both neurons and glia. These findings demonstrate that *Gnb5* heterozygous mice have distinct structural and compositional abnormalities in the hippocampus that may result in altered dentate gyrus functions pertaining to memory formation and spatial navigation.

Disclosures: A. Awe: None. **J. Zhang:** None. **M. Pandey:** None. **P. Adikaram:** None. **W.F. Simonds:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.06/C60

Topic: D.05. Olfaction and Taste

Support: NIH Grant DC000338

Title: Experimental demyelination and synaptic development in the olfactory peduncle

Authors: L. COLLINS, E. VOGT, *P. C. BRUNJES
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Abstract: The olfactory forebrain is interconnected through two large white matter tracts: the lateral olfactory tract (LOT) transfers information from the olfactory bulb to the ipsilateral olfactory cortex while the anterior commissure (AC) interconnects the left and right olfactory cortices. We assessed if these tracts are susceptible to experimental demyelination and, if so, whether they might have the capacity to remyelinate, as suggested by their proximity to the to the subventricular zone. Lysolecithin-induced demyelination and remyelination was examined at multiple post-injection times with electron microscopy. Significant demyelination was seen 7 days post-injection (dpi) and evidence of remyelination was observed by 21dpi in both tracts. The findings indicate that the olfactory system could be an important model for studies of myelin regulation. A second group of studies was prompted by our previous work showing that the tracts develop differently, with the LOT myelinating 2-3 days earlier than the AC. The anterior olfactory nucleus (AON) may reflect the largest effects of these developmental changes as it is the first area to receive information from the LOT and it provides most of the axons that cross in the AC. Four parallel studies were performed to understand general synaptic development in pars lateralis of the AON. First, regional differences in the development of excitatory (VGLUT1 and VGLUT2) and inhibitory (VGAT) terminals were measured. Both VGLUT1 and VGAT endings were very dense. VGLUT1 was evenly spread through all layers while VGAT staining was highest in superficial Layer 1. VGLUT2 synapses were sparse and concentrated just beneath the LOT. Second, perineuronal net staining was observed as early as P5. Brevican was found primarily around pyramidal cell bodies and aggrecan on apical dendrites. Third, an examination of early vascular development indicated that vessel caliber decreases from P5-P30 while density remains the same. Finally, we made a detailed analysis of the terminations of axons coursing through the AC and synapsing in the contralateral AON. Axons were visualized by injections of fluorescent AAV into the right AON. Consistent with previous reports most contralateral labeling occurred in layer 2 of pars lateralis, with progressively less in dorsalis, ventroposterior, and medialis. Reconstructions indicate that contralateral axons are simple with few branch points. Electron microscopic analyses to localize synaptic sites are presently underway.

Disclosures: **L. Collins:** None. **E. Vogt:** None. **P.C. Brunjes:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.07/C61

Topic: D.05. Olfaction and Taste

Support: German Research Foundation Ha4466/11-1

Title: Coordinated electrical activity in the olfactory bulb gates the oscillatory entrainment of entorhinal networks in neonatal mice

Authors: ***S. GRETENKORD**, J. K. KOSTKA, H. HARTUNG, A. MINIER-TORIBIO, I. L. HANGANU-OPATZ
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Abstract: Olfactory inputs from the environment are critical for the survival of newborn mice, but their impact on the development of higher cognitive functions and the limbic system is poorly understood. In contrast to the other sensory systems, which are underdeveloped during the early postnatal period, olfaction reaches full maturity already during intrauterine life and controls mother-offspring interactions. It is, however, still unknown whether early olfactory inputs drive the development of limbic networks. Here, we aim at understanding the structural and functional principles underlying the connectivity and communication between the olfactory bulb (OB) and lateral entorhinal cortex (LEC) - the gatekeeper of limbic circuitry -, during neonatal development. For this, we combine tracing of long-range OB-LEC connectivity with extracellular and patch-clamp recordings from the OB mitral cell layer and LEC in vivo, as well as pharmacological and optogenetic silencing of the OB. We show that discontinuous oscillations with main frequency within the theta band (4-12 Hz) accompany the respiration-related activity in the OB of neonatal mice. They time the firing and synaptic activity of mitral cells. The coordinated activity provides tight coupling by synchrony and directed interactions between OB and LEC. This functional communication relies on early emerging axonal projections of mitral cells to LEC. These findings elucidate the structural and physiological signature of OB-to-LEC communication during early development. Taking into account that LEC drives prefrontal-hippocampal networks during the neonatal period, coordinated activity in the OB might facilitate the maturation of limbic circuitry.

Disclosures: **S. Gretenkord:** None. **J.K. Kostka:** None. **H. Hartung:** None. **A. Minier-Toribio:** None. **I.L. Hanganu-Opatz:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.08/C62

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: RO1DA020140

RO1DC12020

Title: Differential transcription factor expression in two medial amygdala neuronal subpopulations is implicated in components of innate behavioral responses

Authors: *J. E. LISCHINSKY, M. GOODRICH, M. J. HERRERO, J. G. CORBIN
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Abstract: Innate behaviors such as mating and aggression are essential for the propagation of species. The medial amygdala (MeA) is part of the limbic system and is one of the main processing centers for instinctive behavioral cues as it is only two synapses away from olfactory sensory neurons in the vomeronasal organ. Previous work from our laboratory has shown that expression of two transcription factors, Dbx1 and Foxp2, marks two distinct MeA progenitor populations destined to generate two distinct mature subpopulations as defined by molecular and electrophysiological criteria. Furthermore, these populations are both activated during mating and aggressive social behavioral cues, with the latter in a sex-specific manner. In contrast to activation by social cues, *Dbx1*-derived and Foxp2+ neurons are not activated during exposure to non-social cues such as predator odor, which activates another developmentally defined MeA subpopulation. Thus, social versus non-social amygdala responses are predicted by patterns of transcription factor expression at the progenitor stage and may be engaged during different subcomponents of olfactory-driven innate behaviors.

Disclosures: J.E. Lischinsky: None. **M. Goodrich:** None. **M.J. Herrero:** None. **J.G. Corbin:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.09/C63

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: RO1DA020140

RO1DC12020

Title: Foxp2-dependent formation of the social brain

Authors: *M. J. HERRERO[1], M. GOODRICH[1], J. E. LISCHINSKY[1], T. SASAKI[1], C. LAZARSKI[1], Y. IMAMURA[2], K. HASHIMOTO-TORII[1], J. G. CORBIN[1]
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Abstract: *FOXP2*, a transcription factor previously identified as a 'language gene', regulates a variety of autism-linked genes in the cerebral cortex and striatum (e.gs. *Auts2*, *CNTNAP2*, *CTBP1*, *FMR1*, *MET*, *Pax6*, *Plaur* and *SRPX2*). Moreover, *FOXP2* has a score of 3 (suggestive evidence) on the AutDB/SFARI autism scale. However, little is known about the role of FOXP2 in the amygdala, a key part of the limbic system involved in social function. Our recent work revealed that Foxp2+ neurons in the medial amygdala (MeA) are activated by innate reproductive and aggressive behaviors, two social behaviors modulated by olfactory input (Lischinsky *et al.*, *eLife* 2017). Based on these findings we next sought to investigate the identity of Foxp2+ neurons in the MeA and to study how Foxp2 is mechanistically linked to mouse amygdala development and social function. Exploring the identity of MeA Foxp2+ cells in mice, we find that Foxp2+ neurons express several markers related with neuronal development and social behavior. Moreover, RNAseq analysis of FACs sorted Foxp2+ cells revealed high expression of autism-risk genes within this population. Our present data provides a set of indicators for functionally assessing *Foxp2*-driven mechanisms in early development, and amygdala-related social behaviors in adult mice. Deciphering such mechanisms in the amygdala may help to better understand the underlying genetic mechanisms mediating social dysfunction in autism.

Disclosures: M.J. Herrero: None. **M. Goodrich:** None. **J.E. Lischinsky:** None. **T. Sasaki:** None. **C. Lazarski:** None. **Y. Imamura:** None. **K. Hashimoto-Torii:** None. **J.G. Corbin:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.10/D1

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH grant MH078105

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NIH grant MH091645

NIH grant MH086633

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NIH grant MH100029

Title: Developmental outcomes of early adverse care on Amygdala functional connectivity and structure in nonhuman primates

Authors: *E. L. MORIN[1,4,2], K. I. KUITCHOUA[2], B. R. HOWELL[5,4,2], E. J. FECZKO[6,2,3], E. EARL[6], M. PINCUS[4,2], K. M. REDING[7], A. RATLIFF[2], M. STYNER[8], M. SANCHEZ[2,4,3]
[1]Neurosci., [2]Yerkes Natl. Primate Res. Ctr., [3]Ctr. for Translational Social Neurosci., Emory Univ., Atlanta, GA; [4]Dept. of Psychiatry & Behavioral Sci., Emory Univ. Sch. of Med., Atlanta, GA; [5]Univ. of Minnesota, Inst. of Child Develop., Minneapolis, MN; [6]Dept. Of Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR; [7]Section on Integrative Neuroimaging, NIH, Bethesda, MD; [8]Dept. of Psychiatry, Univ. of North Carolina, Chapel Hill, NC

Abstract: Early life stress, including adverse caregiving experiences, is a major risk factor for psychopathology, and social and cognitive deficits. How maltreatment affects neurobehavioral development is not well understood and challenging to disentangle from heritable factors. This study utilized a well-established nonhuman primate model of spontaneous maternal maltreatment (MALT) leading to infant distress. In this model, the highest rates of abuse and rejection co-occur with rapid brain development and limbic maturation, leading to long-term effects on socioemotional behavior, and alterations in amygdala (AMYG) and white matter development. To disentangle the effects of experience from inheritance we used a unique cross-fostering design with random assignment of infants to control or maltreating foster mothers. This study delves into neurodevelopmental alterations underlying behavioral and stress outcomes, focusing on AMYG functional connectivity and structural development in the juvenile period. We collected (1) structural MRI in 42 infant rhesus (20 Control (11 F, 9 M), 22 MALT (8 F, 14 M)) during infancy (2 wks, 3, 6 mo) and juvenile period (12, 18 mo), and (2) resting state functional MRI to examine AMYG functional connectivity (FC) in a subset (13 MALT (6 F, 7 M) and 13 Controls (7 F, 6 M)). We have reported weaker prefrontal cortex-AMYG FC in MALT during development - we extend these studies to examine alterations in AMYG FC to other regions, performing a voxel-wise AMYG seed-based FC analysis at the group level. Stronger positive FC was found in MALT with regions regulating fear and processing socioemotional stimuli: right-left AMYG FC, periamygdaloid ctx, piriform ctx and superior temporal gyrus; brainstem- locus coeruleus, laterodorsal/dorsal tegmental areas, parabrachial complex, Inferior cerebellar peduncle and spinal vestibular nuclei. Stronger negative FC detected with the cerebellum in MALT (all results $p<0.005$, cluster threshold >2 voxels, uncorrected for multiple comparisons). Stronger FC between these regions in MALT suggest increased processing of socioemotional

stimuli, especially related to fear-learning. Fear-potentiated startle studies in these animals, now adolescents, are consistent with this interpretation - MALT show elevated fear potentiated startle, and impaired discrimination of fear and safety cues, suggesting impaired fear regulation. Our group reported larger AMYG volumes in MALT during adolescence associated with increased emotional reactivity - we are extending these studies to examine the emergence of these effects on total brain, gray and white matter, cortical, and hippocampal and AMYG volumes.

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Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.11/D2

Topic: G.03. Emotion

Support: NIH Conte 1P50MH100023

National Primate Research Center base grant RR-00165

Title: Impact of pre-weaning high fructose diet on basolateral amygdala development and socioemotional behavior

Authors: *C. E. BARRETT, A. MENIGOZ, C. BATTERMAN, J. GUO, D. G. RAINNIE
Dept. of Psych. and Beh. Disorders, Emory Univ., Atlanta, GA

Abstract: Type 2 diabetes mellitus (T2DM) is now at epidemic proportions in the US population, with ~10% of the population having T2DM and 35% with pre-diabetic metabolic disorder. The incidence of T2DM in children has risen by > 30%, together with a parallel increase in co-morbid psychological disorders. Children with T2DM are at increased risk of psychiatric disorders, suggesting commonalities in environmental etiology and neural circuitry early in development. Aberrant activity of basolateral amygdala (BLA) principal neurons is thought to be critically involved in the pathophysiology of psychiatric disorders, many of which emerge early in life. We hypothesized that pre-weaning exposure to a high fructose diet (pw-HFrD) would disrupt normative development of BLA principal neurons and be associated with behavioral abnormalities. We examined socioemotional behavior (n=12 males, 12 females per diet group) and single cell BLA gene expression across development in pw-HFrD and control rats. Pw-HFrD lead to a behavioral profile of hyperactivity and increased risk taking as evidenced by increased distance traveled in the open field in males ($p=0.041$), reduced time spent immobile in a forced swim test in both males ($p=0.03$) and females ($p=0.02$) and increased time

in the open zones of an elevated-O maze in males (p=0.001) and females (0.013). pw-HFrD males also displayed reduced startle amplitudes (p=0.018), and females displayed enhanced social interaction time in a social preference test (p=0.0062). Pw-HFrD animals also displayed alterations in genes involved in metabolic regulation in BLA principal neurons. pw-HFrD causes premature expression of insulin and insulin-like growth factor receptor (Igfr) mRNA prior to weaning and abnormally high levels of Igfr mRNA even after weaning. pw-HFrD also causes significant and long-lasting changes to the expression of mRNA for Ampk subunits and other components of the AMPK signaling cascade. Significantly, we have shown that intracellular manipulations of the AMPK pathway regulates electrophysiological properties of BLA principal neurons, and that local AMPK manipulations in vivo alter anxiety-like behavior. Hence, we would predict that disruptions of this pathway during key periods of development resulting from a pw-HFrD would likely result in long-lasting and deleterious effects on emotional processing in the extended amygdala. Uncovering disruptions in metabolic pathways shared between juvenile-onset diabetes and affective disorders may be a crucial step in developing new therapeutic strategies effective at improving the physical and psychological health of those suffering from these metabolic disorders.

Disclosures: C.E. Barrett: None. **A. Menigoz:** None. **C. Batterman:** None. **J. Guo:** None. **D.G. Rainnie:** None.

Poster

655. Limbic System Development

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 655.12/D3

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Title: Immunohistochemical characterization of the rat habenulo-interpeduncular tract during postnatal development

Authors: A. KUMAR, B. VREELAND, *S. E. MCCALLUM
Dept. of Neurosci. and Exptl. Therapeut., Albany Med. Col., Albany, NY

Abstract: The habenulo-interpeduncular pathway (Hb-IPN) serves as a relay station, linking limbic forebrain and midbrain/hindbrain regions, and has emerged as a key circuit in the regulation of nicotine reinforcement, dependence and withdrawal. Major transmitter systems in this pathway include acetylcholine, substance P and glutamate. Recently, expression of the orphan G-protein-coupled receptor, GPR151, has also been identified in this pathway, however a specific function for this receptor is not known, nor has an endogenous ligand been identified. This protein is unique in that it is restricted to the Hb-IPN, a pattern that is highly conserved across multiple species (Broms, et al., Comp. Neurol., 2015). Moreover, genetic deletion of GPR151 causes multiple behavioral deficits in mice and attenuated responses to nicotine

(Kobayashi et al., Front. Behav. Neurosci, 2013).
In this study, we sought to characterize the Hb-IPN pathway throughout postnatal development, using immunohistochemistry. Brains from male and female rats of different ages (postnatal days 2, 5, 8, 14, 21, 35 and adult) were processed for immunohistochemistry and, using confocal microscopy, patterns of GPR151 expression were characterized in the Hb and the IPN. In addition, co-localization of GPR151 with major neurotransmitters abundant in the Hb-IPN (acetylcholine, substance P, and glutamate) was evaluated at the same time points.
Preliminary results reveal differences in GPR151 expression in the Hb-IPN throughout postnatal development. In early postnatal brain (P2), GPR151 expression in the medial habenula (MHb) is localized to the dorsomedial subregion, but emerges in the ventral MHb by P8 and through adulthood. In co-localization studies, differences between early postnatal and adult brain have been observed. Most importantly, little to no co-localization with choline acetyltransferase (ChAT) was observed in the MHb of P2-P8 animals compared to more extensive co-localization of GPR151 and ChAT in the adult MHb. The expression of GPR151 in the lateral habenula (LHb) is higher in brains of P2-P8 rats compared with older rats, but is generally abundant in this region throughout each stage of postnatal development. Consistent with previous findings, (Broms et al., 2015), we found that GPR151 was localized to axons and not found in cell bodies. Despite having no known ligand, GPR151 is a promising pharmaceutical target for multiple conditions, ranging from mood disorders to nicotine addiction. Furthermore, since GPR151 is present in rodent brain as early as E16.5 (Quina et al., J. Neurosci., 2009), it may play a role in mediating developmental responses following prenatal nicotine exposure.

Disclosures: **A. Kumar:** None. **B. Vreeland:** None. **S.E. McCallum:** None.

Poster

656. Comparative Neuroanatomy, Physiology, and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 656.01/D4

Topic: A.10. Development and Evolution

Support: NIH Grant 8TL4GM118977-02

Title: Neural crest derived chromatophores in red-eyed tree frogs

Authors: *P. SANGUANVICHAIKUL[1], A. NKETIAH[2], M. DE BELLARD[3]
[1]biology, California State Unversity Northridge, Panorama City, CA; [3]biology, [2]California State University, Northridge, Northridge, CA

Abstract: The Red-Eyed Tree Frog has striking skin colors that allows it to select mates. Skin coloration comes from neural crest stem cells that give rise to melanocytes and chromatophores. Although chromatophores had been studied in other organisms like chameleons and fish, their

location and phenotype has not been studied in these tree frogs. The purpose of this study is to develop skin histology methods and identify neural crest derived cells. For this, we used immunofluorescence to label different cells within the skin. Thus, we were able to identify poison and mucous glans as well as other neural crest derived cells in the skin of adult frogs. We are beginning to collect similar samples from tadpoles and froglets. We plan to continue mapping the histology during the different stages of development and eventually cell cultures. By doing so, we can follow the development of melanocytes and chromatophores.

Disclosures: **P. Sanguanvichaikul:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); National Institute of Health. **A. Nketiah:** None. **M. de Bellard:** None.

Poster

656. Comparative Neuroanatomy, Physiology, and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 656.02/D5

Topic: A.10. Development and Evolution

Support: Sharon Stewart Aniridia Research Trust

Bio-Imaging Research Center

Franklin Foundation Neuroimaging Fellowship

NIH Shared Instrumentation grant S10RR023706

Title: PAX6-dependent changes in the adult mammalian brain

Authors: *M. K. GRANT[1], A. M. BOBILEV[3], A. E. BRANCH[4], J. B. BYERS[1], K. HEKMATYAR[2], J. D. LAUDERDALE[1]
[1]Cell. Biol., [2]Bio-Imaging Res. Ctr., Univ. of Georgia, Athens, GA; [3]Psychiatry, Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [4]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: Aniridia is a congenital and progressive disorder affecting approximately 1 in 83,000 live births. Although the disorder is most well known for its ocular phenotypes, the condition has several other abnormalities, which are only recently emerging as prominent features of the disorder. These include neural, sensory, cognitive, and auditory processing deficits. Development of aniridia in humans is predominately caused by heterozygous loss-of-function mutations in the *PAX6* gene, a highly conserved transcription factor critical for normal eye and brain development. Previous studies of patients with aniridia using magnetic resonance imaging (MRI) have shown changes in interhemspheric connectivity and grey matter volume. Our lab has

utilized 3T MRI to show structural changes in the brains of aniridia patients as compared to their *PAX6*-normal comparisons. Consistent with other reports, we found reductions to major fiber tracts such as the anterior commissure, posterior commissure, and optic chiasm in addition to lack of or reduction of the pineal gland. The cellular basis for these changes are not well understood. To better understand the role of *PAX6* in brain development and adult brain function we have turned to the rodent model of aniridia, *Small eye*, where we can utilize a variety of tools to assess *Pax6* expression and the neural consequences of mutations in the brain. The current study employed MRI using a 7T Agilent system to acquire structural brain images using 3D T2 weighted fast spin echo sequences, histological examination, *Pax6* transgenic mouse lines, histological examination, and tissue clearing of the adult brain to examine the consequences of loss of one functional copy of the *Pax6* gene. Results indicate that the effect of *Pax6* mutations on discrete brain structures such as the anterior commissure and optic chiasm are conserved from mice to humans. Furthermore, our imaging of transgenic brains using clearing methods has allowed us to develop a novel analysis comparing adult *Pax6* expression directly with structural changes in *Small eye* heterozygous mice. Collectively, these data allow us to visualize the overlap between adult *Pax6* expression and structural brain variants, and provide new hypotheses regarding the effects of early versus adult *PAX6* haploinsufficiency in the mammalian brain. Implementation of this approach also provides a novel platform for investigating the link between gene expression and neural structure and connectivity, with broad applications for neurogenetic research.

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Poster

656. Comparative Neuroanatomy, Physiology, and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 656.03/D6

Topic: A.10. Development and Evolution

Support: Deanship of scintific research - Universiy of Jordan

Title: Gender Differences of axonal density in the Rat Corpus Callosum

Authors: *D. J. AL QATTAN[1], L. ALZGHOUL[2], M. ELBELTAGY[3], A. AL-SHATARAT[3]
[1]Pathology, [2]Dept. of Physiol. and Biochem., The Univ. of Jordan, Amman, Jordan; [3]Dept. of Anat., The university of Jordan, Amman, Jordan

Abstract: Sexual dimorphism exists at all levels of the nervous system, from genetic, anatomical, and system levels. These sex differences could underlie gender-related differences in behavior and neuropsychological function, as well as, the sex differences in the prevalence of

various mental problems such as autism, attention deficit, and schizophrenia. The corpus callosum (CC) is the largest of the brain commissures, which connects the cerebral cortices of the two hemispheres, and provide interhemispheric connectivity for information transfer and processing between cortical regions. Alteration in the axonal density of CC will alter interhemispheric connectivity and commonly documented in several psychiatric disorders. The CC consists of myelinated and unmyelinated axons, glial cells, and blood vessels. Several functional studies have reported that CC function is associated with its axon density and myelination properties. The sexual dimorphism in the axonal content of the CC has always been controversial; hence, the aim of this study was to analyze the differences in axons density of the CC between male and female rats. To assess that, five pairs of adult male and female rats were perfused and the CC was sectioned. Then four sections from different subregions of the corpus callosum that represent the genu, anterior body, posterior body, and splenium of the CC were stained and electron microscopic images were captured using stereological guidelines. Later, the axons density for each subregion is calculated and compared between males and females. Our preliminary findings of the present study indicated region specific differences in the myelinated, unmyelinated or the ratio of myelinated/total axons in the CC between male and female rats.

Disclosures: D.J. Al Qattan: None. **L. Alzghoul:** None. **M. ElBeltagy:** None. **A. Al-Shatarat:** None.

Poster

656. Comparative Neuroanatomy, Physiology, and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 656.04/DP09/D7 (Dynamic Poster)

Topic: F.01. Neuroethology

Support: NIH Grant NS090296

Title: Structural and functional brain changes due to activity-dependent myelination

Authors: *R. T. REUSCH[1], A. RIGODANZO[1], C. SHERWOOD[3], K. A. PHILLIPS[2]
[1]Neurosci., [2]Psychology, Trinity Univ., San Antonio, TX; [3]Anthrop., George Washington Univ., Washington, DC

Abstract: Changes in white matter organization and reorganization of functional connectivity networks are hypothesized to result from activity-dependent myelination. We used non-invasive diffusion weighted imaging and resting-state fMRI to identify structural and functional brain changes associated with time engaged in motor learning. Ten socially housed capuchin monkeys (*Cebus apella*), naïve to prior fine motor tasks, participated in the 12-week experiment. Five monkeys (male $n = 3$) trained daily on a fine motor task (Peg Board) for 8 weeks followed by 4 weeks of continued once-a-week practice; the control condition of five monkeys (male $n = 2$) did

not engage in a fine motor task. Neuroimages were collected from all monkeys at three time points: baseline, 8 weeks, and 12 weeks. Tract based spatial statistics will be used to evaluate changes in the white matter underlying the intraparietal sulcus. Seed-based analysis approach will evaluate changes in the resting-state connectivity visuospatial and sensorimotor networks. We hypothesize that subjects will show an increase in 1) structural integrity of myelin (quantified by fractional anisotropy, FA) and 2) strength of associated functional networks after engaging in motor learning. Furthermore, we expect changes in FA and functional networks are positively correlated with each other.

Disclosures: R.T. Reusch: None. **A. Rigodanzo:** None. **C. Sherwood:** None. **K.A. Phillips:** None.

Poster

656. Comparative Neuroanatomy, Physiology, and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 656.05/D8

Topic: F.05. Neuroimmunology

Support: OD010996

Title: Lack of vagal parasympathetic innervation of the spleen in different strains of rats

Authors: *G. CANO, S. HERNAN, A. F. SVED
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Abstract: Activation of splenic sympathetic nerves plays an important role in the anti-inflammatory responses orchestrated by the spleen in rodents. Nevertheless, an alternative mechanism has been proposed in which vagal parasympathetic nerves innervate the spleen and have anti-inflammatory actions. This route is controversial because only sympathetic innervation of the spleen has been documented. It has been proposed that the spleen receives direct vagal parasympathetic innervation exclusively at its tips (apparently missed in previous tracing studies). To explore this possibility, we injected two recombinants of the viral transneuronal tracer Pseudorabies virus that express RFP (PRV-614) and GFP (PRV-152) simultaneously into the tips of the spleen (2 ul each), or in the tip and main body of the spleen (4 ul), respectively. To examine if there were anatomical differences in the spleen innervation among different rat strains or vendors, we used Sprague-Dawley rats from two vendors, and Long-Evans rats. Rats were perfused after several specified survival times, and brains and spinal cords removed and processed immunohistochemically to detect both viruses.
Macroscopically, we observed a fiber-like structure in the upper tip of the spleen (very prominent in Harlan Sprague-Dawley rats), which runs independently of the vasculature and ends on the stomach surface. This structure is most likely the equivalent of the gastrosplenic

ligament in humans. Microscopically, early infection was observed in sympathetic preganglionic neurons (SPNs) located in the intermediolateral cell column (IML) of the spinal cord (T_{3-12}). The majority of infected SPNs were single infected, though some double infected SPNs were observed in IML clusters. At intermediate survival times, infected neurons appeared in other spinal groups, as well as in brain regions containing neurons known to innervate the IML, such as the paraventricular hypothalamic nucleus, A5 group, rostroventrolateral medulla, ventromedial medulla and caudal raphe nucleus. The majority of brain infected neurons were double infected. At longer survival times, infected neurons appeared in additional brain regions and were mostly double infected. There were no infected neurons in the dorsal motor nucleus of the vagus at any survival time analyzed in any rat strain tested, demonstrating the lack of vagal parasympathetic innervation at the tips of the spleen as previously proposed. Our anatomical results suggest that the effects of vagal stimulation on splenic function in rats are not mediated by direct vagal innervation of the spleen, but most likely by an alternative indirect mechanism that needs to be elucidated.

Disclosures: G. Cano: None. **S. Hernan:** None. **A.F. Sved:** None.

Poster

656. Comparative Neuroanatomy, Physiology, and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 656.06/D9

Topic: A.10. Development and Evolution

Title: Climatic / environmental stress responses of apis mellifera in the tropics

Authors: *S. FELICIANO[1], T. GIRAY[1], J. AGOSTO[2], M. ALI DÖKE2[3], F. NOEL[2], D. LOUBRIER[2], M. SERPA[2]
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Abstract: Organisms have developed physiological and behavioral strategies to survive environmental extremes, such as changes in temperatures, food shortages, and precipitation. In temperate regions, the honey bee, *Apis mellifera*, has the capacity to survive the low temperatures during winter producing bees called “winter bees”. For this study we specifically examined whether the *A. mellifera* uses similar strategies to cope with the stress of low food availability and lower night temperatures in the tropics. To test the hypothesis that “winter bee” physiology is a general response to adverse conditions, we examined bees in Puerto Rico, a tropical island with relatively warm temperatures year-round. Yet in dry and wet seasons there occurs changes in food availability (plants blooming changes over the year). We have demonstrated that genetically distinct, Africanized bees in Puerto Rico demonstrate a decrease in

the colony brood amounts with reduced temperature (75 degrees F vs 90 degrees F in wet season), and reduced flowering of forage plants (15% in bloom from November to February). We also examined individual characteristics associated with winter bees such as high longevity under adverse conditions. We examined in Puerto Rican bee's expression of physiological traits and genes that are correlated with overwintering bees in the temperate zone.

Disclosures: S. Feliciano: None. **T. Giray:** None. **J. agosto:** None. **M. Ali Döke2:** None. **F. noel:** None. **D. Loubrier:** None. **M. Serpa:** None.

Poster

656. Comparative Neuroanatomy, Physiology, and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 656.07/D10

Topic: B.09. Physiological Properties of Neurons

Title: The cooperation between Tip60 HAT activity and transcription factories in activity-dependent genome reorganization

Authors: *A. KARNAY[1], F. ELEFANT[2]
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Abstract: Coordinated transcription of genes within mammalian nuclei in response to external stimulus is a dynamically orchestrated process involving the interplay between epigenetics-mediated chromatin remodeling and RNA polymerase-mediated transcription. Recently, the potential for an additional layer of regulation has emerged in which active, co-regulated genes converge and relocalize within specialized nuclear subcompartments enriched in hyperphosphorylated RNAPII and transcriptional regulatory proteins thereby mediating efficient, co-regulated gene transcription. While these nuclear 'hot spots' known as transcription factories (TFs) have been demonstrated in other cell types, its presence in hippocampal neurons and its role in activity-dependent transcriptional control within the brain remains relatively unexplored. Furthermore, while previous findings indicate a functional relevance of histone acetylation in activity-dependent gene expression, the full array of HATs involved in this process remain to be determined. To gain insight into this process, we utilized rat hippocampal cells and analyzed Tip60 histone acetyltransferase (HAT)-mediated histone acetylation changes in known co-regulated cognition-associated genes before and after extracellular stimulation. Our findings thus far show that Tip60 shuttles into the nucleus following external stimulation and associates with genes with well characterized roles in synaptic plasticity to induce their co-activation. We are currently characterizing potential changes subcellular nuclear localization and interaction between these genes and transcription factories before and after stimulation-induced expression using FISH analysis. Our findings should provide fundamental insights into a new physiological

gene expression paradigm governing transcriptional activation of co-regulated genes within neuronal nuclei in response to external stimuli and how disruption of this process may contribute to the etiology of neurodegenerative disease.

Disclosures: A. Karnay: None. **F. Elefant:** None.

Poster

656. Comparative Neuroanatomy, Physiology, and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 656.08/D11

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH NIGMS R01GM095653

Stanford Anesthesia

Title: Generation of neocortical oscillations in isolated brain slices

Authors: B. A. DAGNE[1], N. S. CAYLA[1], S. W. EVANS[2], *B. MACIVER[3]
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Abstract: Introduction: The electroencephalogram (EEG) is a commonly used measure of electrical activity in the brain. Synchronous rhythmic activity and modulations of such oscillations with behavior has been useful for understanding complex processing of stimuli in the brain. *In vitro* studies have played an important role in helping us to better understand how these rhythms are generated. Different frequencies of oscillatory activity have been induced in rodent neocortical slices by pharmacologically mimicking cholinergic inputs to the cortex.
Methods: Micro-EEG were recorded from 400 µM-thick rat brain slices submerged in artificial cerebrospinal fluid (ACSF) by placing stimulating electrodes in white matter and recording electrodes in layers II/III of the neocortex in OC2mm cortex. We stimulated cortical neurons electrically to drive thalamic and cortical inputs; and chemically by adding combinations of carbachol (cholinergic agonist), bicuculline (competitive antagonist of $GABA_AR$), and kainate (agonist of non-NMDA glutamatergic receptors), which variably activated glutamatergic or cholinergic pathways. Also, 2-amino-5-phosphonovaleric acid (APV, an NMDA receptor antagonist) was used to tease apart glutamatergic mechanisms.
Results: *In vivo*-like theta oscillations were produced in the slices by mimicking cholinergic and GABAergic inputs with combined applications of carbachol, and bicuculline. Also, activating glutamatergic inputs through the addition of kainate and carbachol also produced theta oscillations without involving any GABAergic disinhibition. Lowering magnesium concentrations in the ACSF increased NMDA-gated glutamate inputs and this produced even

more robust theta oscillations. Finally, the necessity of NMDA stimulation was shown when APV was added to reversibly block the oscillations produced by any combination of agents. **Conclusions:** This project provides a pharmacological survey of agents for creating EEG oscillations in the neocortical slices. Application of drugs influencing glutamatergic and cholinergic receptors can stimulate oscillatory activity in the neocortex. Moreover, it is possible to induce theta oscillations without disturbing GABA activity, by co-activating kainate receptors. This will be useful to study drugs that involve effects on GABAergic inhibition.

Disclosures: B.A. Dagne: None. **N.S. Cayla:** None. **S.W. Evans:** None. **B. MacIver:** None.

Poster

656. Comparative Neuroanatomy, Physiology, and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 656.09/D12

Topic: A.02. Postnatal Neurogenesis

Support: NIH grant ES 013885

Title: Estradiol and dihydrotestosterone regulation of "muscle" genes during sexual differentiation of neural structures

Authors: K. CLEMENTS, *S. L. PETERSEN
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Abstract: Hormonal regulation of neural development contributes to sexual dimorphism of brain structures and functions that become apparent in adulthood. According to existing dogma, perinatal males are exposed to testosterone released by the developing testes, and estradiol (E2) derived from testosterone is the hormone that controls sexual differentiation. Two examples of such sexually dimorphic brain regions are the anteroventral periventricular nucleus (AVPV) and the hippocampus. These regions express both androgen and estrogen receptors, and ligands of these receptors, dihydrotestosterone (DHT) and E2, regulate expression of numerous genes that may play a role in sexual differentiation. We previously showed that the genes differing most dramatically between males and females in the postnatal day 2 (PND2) AVPV are actin-binding proteins previously thought to be muscle-specific. Males express higher levels of mRNAs encoding titin (Ttn), myosin heavy chain 2 (Myh2), troponin C1 (Tnnc1), nebulin (Neb) and advilin (Adv) among others. To determine whether expression of these genes is regulated by sex hormones, PND1 female rats were injected with vehicle or 10 ng of DHT, E2 or combined DHT and E2 (n=8-11/group). On PND2, we microdissected AVPV and hippocampal tissue from the brains of these animals and used qPCR to measure mRNA levels of the genes of interest. Of the 5 genes examined, DHT upregulated Ttn, Myh2, Tnnc1 and Neb, but not advilin. E2 also increased expression of the same genes, except Myh2. However when DHT and E2 were

combined, there was no additive effect. In the hippocampus, DHT upregulated the expression of Tnnc1, Myh2, Ttn, but not Neb. E2 had no effect on expression of these genes in hippocampus but diminished the effect of DHT when both hormones were administered together. While the neural function of these "muscle" genes are currently unknown, their regulation by hormones indicate they may play a role in the development of sexual dimorphisms in the brain. Our results also support the idea that androgens and the androgen receptor may be important for sexual differentiation of neural structures.

Disclosures: K. Clements: None. **S.L. Petersen:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 657.01/D13

Topic: B.03. G-Protein Coupled Receptors

Support: Fundación Gonzalo Río Arronte- IAP

NIH grant No.NS036607 (CNA).

Title: Mexneurin-1 peptide bioactivity in the rat CNS

Authors: *P. LEFF[1], M. E. MATUS-ORTEGA[2], A. SALAZAR-JUÁREZ[2], J. C. CALVA-NIEVES[2], B. PENG[3], J. E. PINTAR[3,4], H. S. GOMPF[4], C. N. ALLEN,[4], B. ANTON[2]
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Abstract: Opioid peptides comprise a family of active neuropeptides and neurohormones that are processed from large precursor proteins. An immunoscreening, using affinity-purified rabbit antisera against synthetic μ-opioid agonists−.endomorphins (EM1, EM2) on a whole mouse brain cDNA library, led to the identification a novel protein precursor named as proMexneurin. This latter encodes three different peptide sequences referred as to Mexneurin-1 (Mx-1) (an endomorphin-like peptide), Mexneurin-2 (Mx-2), and Mexneurin-3 (Mx-3). Mx-1 peptide motif shares similar conserved regions with EM1 and EM2, respectively. We explored the hypothesis that Mx-1 might display electrophysiological activity in hypothalamic regions known to respond to μ-opioid agonists. 12 cells recorded from the SCN (shown to be largely unresponsive to μ-agonists) did not respond to Mx-1 by reducing the spontaneous firing rate (SFR). Conversely, 32 out of 99 cells in the rostral subdivision of the SON responded to Mx-1. SFR was strongly

inhibited in response to focal application of Mx-1, similar to EM1. A Mx-1 dose-related response was found after 85 neurons were recorded in a whole cell mode, of which 28 responded with an evoked (outward) current in a dose-dependent fashion (10 nM to 100 µM; EC_{50} = 76.6 nM) (holding a depolarized membrane potential at -50 mV). To examine whether Mx-1 acts through the µ receptor, we tested whether CTOP (100 nM) could inhibit the response to Mx-1(100 nM). Six neurons from SON were allowed to maximally respond to bath application of Mx-1 (42.2 ± 7.2 pA) and CTOP (100 nM) reduced the current amplitude gradually to 3.8 ± 2.0 pA. After antagonist washout, Mx-1 mediated currents returned to 31.0 ± 8.3 pA. To assess the agonist efficacy of Mx-1 on µ-opioid receptors, we measured GPCR activation by direct activation of Gα subunits using [^{35}S]GTPγS binding. Mx-1 stimulated the incorporation of [^{35}S]GTPγS in rat hippocampus membranes, displaying a range of potency and intrinsic activity in a concentration-dependent manner, with a maximal stimulation of 86% over baseline values at 0.6 µM. Naloxone (10 µM) inhibited the Mx-1-inducing the incorporation of γ-GTP. Mx-1 K-conductances evoked electrophysiological responses as a result of µ receptor activation in specific brain regions (i.e., SON) which were sensitivity to µ-opioid antagonists (CTOP) as well to µ-opioid agonists (EM1) among others. [^{35}S]GTPγS stimulation by Mx-1 proposed a binding activity on hippocampal µ-opioid receptors, an effect inhibited by naloxone. Taken together, these results argues in favor of a putative role of this novel peptide as an endogenous µ-opioid receptor agonist in the brain.

Disclosures: **P. Leff:** A. Employment/Salary (full or part-time):; National Institute of Perinatology. Mexico City 11000. **M.E. Matus-Ortega:** A. Employment/Salary (full or part-time):; Department of Neuroscience and Cell Biology, Rutgers Biomedical and Health Sciences, Newark, NJ, USA.. **A. Salazar-Juárez:** None. **J.C. Calva-Nieves:** None. **B. Peng:** None. **J.E. Pintar:** None. **H.S. Gompf:** None. **C.N. Allen,:** None. **B. Anton:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 657.02/D14

Topic: B.03. G-Protein Coupled Receptors

Support: FONDECYT grant N° 1150244

CONICYT PhD fellowship to HEY

Title: Type-2 corticotropin releasing factor receptor modulates the synapse between basolateral amygdala and prefrontal cortex

Authors: *H. E. YARUR, I. M. VEGA-QUIROGA, K. GYSLING
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Abstract: Basolateral amygdala (BLA) and prefrontal cortex (PFC) are involved in the modulation of the stress response. Neuronal activity in PFC is reduced when stressful events occur (García et al, 1999). In addition, exposure to stressful events blocks the induction of LTP in the BLA-PFC synapse (Maroun & Richter-Levin, 2003). Drugs of abuse use similar structures and neurotransmitters to those involved in the stress response, such as PFC, ventral tegmental area (VTA) and amygdala, and neurotransmitters such as corticotropin-releasing factor (CRF) and dopamine. There is evidence that type-2 CRF receptor (CRF2) (Guan et al, 2014) and the dopamine D1 receptor (DAD1) (Sanchez et al, 2003) in PFC are involved in relapse to the compulsive search for drugs of abuse. Considering the available evidence, we decided to study whether CRF2 and DAD1 are involved in the neurochemical regulation of the BLA-PFC synapses. The experiments were performed in anesthetized rats in which the BLA was stimulated by a depolarizing solution and extracellular levels of glutamate in the PFC were analyzed by in vivo microdialysis in the presence or absence of pharmacological antagonists for CRF2 and DAD1 receptors. The results showed that the stimulation of BLA increases glutamate extracellular levels in PFC. The intra PFC infusion of antisauvagine-30, a CRF2 antagonist, significantly increased PFC glutamate extracellular levels induced by BLA stimulation. In contrast, the intra PFC infusion of SCH23390, DAD1 antagonist did not cause significant changes in PFC glutamate levels after BLA stimulation. The results suggest that the activation of CRF2 but not DAD1 in PFC reduces the release of glutamate induced by BLA stimulation.

Disclosures: H.E. Yarur: None. **I.M. Vega-Quiroga:** None. **K. Gysling:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 657.03/D15

Topic: B.03. G-Protein Coupled Receptors

Title: The role of GPR139 in dopamine D2 receptor signaling

Authors: *L. WANG, G. LEE, P. BONAVENTURE, T. LOVENBERG, C. LIU
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Abstract: Previously, we reported that GPR139, an orphan G-protein coupled receptor (GPCR), is activated by the essential amino acids L-tryptophan (L-Trp) and L-phenylalanine (L-Phe) via Gαq- coupling. GPR139 is highly expressed in the pituitary and central nervous system including habenula, septum, striatum and zona incerta, which are known regions involved in mood regulations. Trp and Phe have been used for the treatment of mood disorders. It was believed that administration of Trp or Phe (which are substrates for synthesis of neurotransmitters such as serotonin, dopamine, and adrenaline) may elevate the levels of these neurotransmitters in the brain and then improve the mood. The finding of GPR139 as the receptor for Trp and Phe

strongly suggests that the therapeutic effects of Trp and Phe may be due to the activation of GPR139. However, the exact physiological roles of GPR139 remain to be studied. RNA-seq studies showed that GPR139 mRNA expression has the very similar pattern to that of dopamine D2 receptor, which is the target for many antipsychotics. We wonder whether GPR139 participates in the functions of D2 receptor. The aim of this study is to investigate the role of GPR139 in the signaling modulation of D2 receptor in vivo and in vitro.

Disclosures: L. Wang: None. **G. Lee:** None. **P. Bonaventure:** None. **T. Lovenberg:** None. **C. Liu:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

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Program#/Poster#: 657.04/D16

Topic: B.03. G-Protein Coupled Receptors

Support: FONDECYT grant N° 1150244

Title: Structural characterization of the heteromer between D1 dopamine and type 2-alpha corticotropin releasing hormone receptors

Authors: *C. A. LOPEZ, H. YARUR, B. COLOMA, K. GYSLING
Fac. of Biol. Sciences, Dept. of Cell. and Mol. Biol., Pontificia Univ. Catolica De Chile, Santiago, Chile

Abstract: A recent study showed that D1 dopamine (D1R) and type 2-alpha corticotrophin releasing hormone (CRHR2α) receptors are capable of heterodimerizing in living cells, interacting physically and functionally (Fuenzalida et al, 2014). It was shown that this interaction produces a change in signaling of D1R and sub-cellular localization of both receptors. CRHR2α is mainly located intracellularly, however when is co-expressed with D1R increases its presence on the plasma membrane. On the other hand, D1R that is mainly at the plasma membrane but it increases its intracellular location when co-expressed with CRHR2α. The aim of the present work is to determine the structural basis of the D1R/CRHR2α heteromer formation. To this end, we generated a D1R mutant, and chimeras between CRHR2α and the type b2 γ-aminobutyric acid metabotropic receptor (GABAb2). First, we mutated a di-leucine motif of the D1R C-terminal domain (D1R-mut). It has been reported that this mutation retains D1R intracellularly (Guo et al, 2011). The results show that the co-expression of D1R-mut with CRHR2α does not modify the localization of CRHR2α. These results suggest that the D1R / CRHR2α heteromer is formed intracellularly. Next, in order to reveal the domains involved in the formation of the D1R/CRFR2 α heteromer, we generated receptor chimeras exchanging the transmembrane domains 4, 5 or 6 (TM4, TM5 or TM6) of CRHR2α by the corresponding domains of GABAb2.

The exchange of TM4 or TM5 of CRHR2α reduces the amount of D1R/CRHR2 complex. Thus, our preliminary data suggest that TM4 and TM5 of CRHR2α are necessary for the interaction between both receptors. Altogether, our results confirm that D1R/CRHR2α heteromerize and add novel evidence regarding the possible domains involved in their physical interaction. The existence of the heteromer could constitute a new therapeutic target for the treatment of addiction to drugs of abuse and the knowledge the structural basis of their interaction should help to develop new ligands.

Disclosures: C.A. Lopez: None. **H. Yarur:** None. **B. Coloma:** None. **K. Gysling:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

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Program#/Poster#: 657.05/D17

Topic: B.03. G-Protein Coupled Receptors

Support: JSPS KAKENHI 26460709, 17K09045

Title: Identification of two nocistatin-binding proteins by using a novel photoaffinity probe

Authors: *M. HARADA[1], T. MINAMI[2], S. ITO[3], E. OKUDA-ASHITAKA[1]
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Abstract: Nocistatin (NST) is a neuropeptide produced from the same precursor protein of nociceptin/orphanin FQ (N/OFQ). N/OFQ is involved in a broad range of central functions including pain, learning, memory, anxiety, and feeding via selective binding to its receptor. On the other hand, NST has opposite effects on various central functions evoked by N/OFQ. Although the receptor for N/OFQ has been shown to be highly homologous to opioid receptors, the composition and structure of the receptor(s) for NST remain unclear. In the present study, we identified two NST-binding proteins by using a novel NST photoaffinity probe (Pb-NST). The Pb-NST, kindly provided by Nippon Shinyaku Co. Ltd., contains an azide moiety for the tagging of NST binding protein as well as biotin for protein detection and visualization. Intrathecal administration of the Pb-NST inhibited the N/OFQ-evoked tactile pain allodynia with a half-maximal inhibitory dose (ID_{50}) of 500 fg in a manner similar to that of free bovine NST (ID_{50}=700 fg). Following incubation with mouse spinal cord slices, the Pb-NST-binding proteins were visualized with Alexa488-conjugated streptavidin. Fluorescence analysis indicated that the Pb-NST-binding proteins were primarily localized in the gray matter of the spinal cord. Furthermore, the fluorescence intensity consistently increased over time by Pb-NST in a concentration-dependent manner ranging from 0.1 nM to 1 μM. After photo-crosslinking of the

Pb-NST-protein complex, the protein lysate was separated by gel electrophoresis. Subsequent western blot analysis using a horseradish peroxidase-conjugated streptavidin revealed two dominant Pb-NST-binding protein bands at 58 and 64 kDa. Furthermore, the binding of these proteins to Pb-NST was displaced with an excess amount of unmodified NST. Taken together, these results suggest that there are two proteins (58 and 64 kDa) expressed in the gray matter of the spinal cord that can bind to NST.

Disclosures: M. Harada: None. **T. Minami:** None. **S. Ito:** None. **E. Okuda-Ashitaka:** None.

Poster

657. Peptide Receptors

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Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant DA024746

NSFC Key Program 21135005

NSFC Grant 81402806

Title: A receptor-specific crosstalk between the prostanoid 3 and the Bombesin sub-type 3 receptors

Authors: *Y. ZHANG[1], Y. LIU[2], Z. WANG[3], X. ZHANG[2], A. ALACHKAR[4], X. LIANG[2], O. CIVELLI[5]
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Abstract: Bombesin receptor subtype-3 (BRS-3) is an orphan G protein-coupled receptor that does not exhibit high affinity for bombesin or the endogenous peptides of the other receptors part of the same subfamily. It is present in the central nervous system, peripheral tissues and in tumors; our understanding of its role in normal physiology/pathophysiology is limited because we lack the identity of its natural ligand. In an attempt to identify this ligand, we screened toad skin extracts and identified prostaglandins as putative ligands. In BRS-3 transfected HEK293 cells we show that prostaglandins, PGE2 being the most potent, fulfill the pharmacological criteria of affinity, selectivity and specificity to be considered as agonists to the BRS-3 receptor. However, we also found that PGE2 was unable to activate BRS-3 in different cellular environments (CHO and Hela cells). We suspected that endogenous prostanoid receptors (EPs) in these environments may be the cause of this cellular selectivity. In particular we found that EP_3 are expressed in HEK293 but not CHO cells. Consequently we set up to reconstitute the

HEK293 environment in CHO cells and found that BRS-3 and EP_3 interact to potentiate PGE2 signaling. This potentiating effect is receptor specific and occurs only when BRS-3 is paired to EP_3 and not other receptor. This represents an example of functional cross-talk between two distantly related GPCRs and may be of clinical importance for BRS-3 targeted therapies.

Disclosures: Y. Zhang: None. **Y. Liu:** None. **Z. Wang:** None. **X. Zhang:** None. **A. Alachkar:** None. **X. Liang:** None. **O. Civelli:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 657.07/D19

Topic: B.03. G-Protein Coupled Receptors

Title: Hypothalamic miR-132-3p changes in response to intracerebroventricular oxytocin: Relevance for anxiety- and fear-related behaviour

Authors: *A. BLUDAU[1], R. MENON[1], G. MEISTER[2], I. D. NEUMANN[1]
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Abstract: miR-134 and the miR-132/212 family are highly abundant in the brain and known to be crucial regulators of neural plasticity and function. Their dysregulation is implicated in various neurodegenerative and affective diseases. The neuropeptide oxytocin (OXT) reduces anxiety and stress responses when administered to the rat paraventricular nucleus (PVN) of the hypothalamus. However, the underlying molecular mechanisms of OXT receptor (OXTR) signalling in the context of anxiety- and fear-alleviating properties are not well understood. Therefore, we studied the effects of synthetic and endogenous OXT on miRNA level within the PVN of Wistar rats in the context of anxiety-related behaviour.
Deep Sequencing of the rat PVN revealed numerous miRNAs that are changed in their expression in response to acute intracerebroventricular (icv) OXT. Further validation of Deep Sequencing showed an up-regulation of miR-132-3p levels within the PVN of male and female rats 3h after icv OXT, whereas miR-212-3p and miR-134-5p remained unchanged. In males, this effect was seen in a region- and time-specific manner, since no expression changes of miR-132/212 family members were observed in the prefrontal cortex or amygdala 3h after icv OXT and no changes were seen in all studied brain regions 90min after icv OXT.
To further evaluate the effect of endogenous OXT on miRNA expression within the PVN, lactating dams, which are characterized by high availability of OXT in the brain, were compared with virgins and dams without pups for time periods of either 4h or 24h. However, all aforementioned miRNAs were found to be unchanged in the PVN of lactating rats compared to virgins. In support, blockade of endogenous OXTR signalling during lactation by a selective

OXTR antagonist did not change miR-132-3p, or miR-212-3p level. However, separation of the dams from their pups for 4h increased miR-132-3p levels in the PVN in comparison to virgins. Moreover, a 4h separation period tended to increase the expression of this particular microRNA compared to dams with a 24h separation period, possibly indicating an effect of acute maternal stress on intra-PVN miRNA levels. This data reveals a possible gender-independent regulation of miR-132-3p by acute synthetic OXT.
Moreover, chronic availability of endogenous OXT may involve miR-132-3p regulation within the PVN. Generally, OXT also acts within the lateral septum (LS), where it was found to reverse social fear induced by the social fear conditioning paradigm in mice. Therefore, we are currently evaluating miRNA levels within the LS in socially fear-conditioned mice and specifically the role of miR-132-3p in social fear-related behavioural regulation.

Disclosures: **A. Bludau:** None. **R. Menon:** None. **G. Meister:** None. **I.D. Neumann:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 657.08/D20

Topic: B.03. G-Protein Coupled Receptors

Support: MOST 104-2314-B-002-053-MY3

MOST 104-2923-B-002-006-MY3

MOST 106-2321-B-002-019

Title: Involvement of neuropeptide S, orexin and endocannabinoid in stress-induced cocaine relapse in mice

Authors: *L.-C. CHIOU[1,2], Y.-H. CHOU[3]
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Abstract: The high prevalence of drug relapse severely limits the success of drug rehabilitation programs. Among the relapse initiators, stress in an inevitable inducer in the daily life of extinguished addicts. Recently, we have disclosed a novel mechanism for stress-induced cocaine relapse, i.e. stress can activate the orexin 1 receptor (OX1R) in the ventral tegmental area (VTA) and, via the phospholipase C (PLC) and diacylglycerol lipase (DAGL) enzymatic cascade, generate 2-arachidonolyglycerol (2-AG), an endocannabinoid that inhibits GABAergic transmission in VTA dopamine neurons, resulting in cocaine relapse[1]. Here, we revealed a novel player, neuropeptide S (NPS), a 20 amino acid-containing neuropeptide named by its evolutionally conserved N-terminal serine residue, in this sequential cascade. It was initiated

based on previous findings that 1) stress activated the NPS-containing neurons in the peri-locus cereous (LC) and the parabrachial nucleus (PBN); 2) stress also activated orexin neurons in the lateral hypothalamic (LH); 3) intra-LH microinjection of NPS activated hypothalamic orexin neurons. We used a three-day bias cocaine-conditioned place preference (CPP) paradigm to induce cocaine seeking. The cocaine CPP scores were measured at pre-conditioning, cocaine-conditioning, extinction and reinstatement stages. As reported previously[1], a 30-min acute restraint stress significantly reinstated extinguished cocaine CPP in mice, i.e. inducing cocaine relapse. This stress-induced cocaine relapse was prevented when SHA 68, an NPS receptor antagonist, was *i.p.* administered in mice before restraint stress. Besides, *i.c.v.* injection of NPS significantly reinstated extinguished cocaine CPP in mice. NPS (*i.c.v.*)-induced cocaine relapse was prevented by *i.p.* pretreatment with SHA 68, SB334867 (an OX1R antagonist) or AM 251 (a CB1R antagonist). Furthermore, NPS (*i.c.v.*) increased the orexin A level in the mouse VTA in a manner prevented by SHA 68. These results suggest that during stress, NPS neurons in the PBN and/or peri-LC in mice are activated, releasing NPS that activates orexin neurons via NPS receptors in the LH, releasing orexins that, via OX1Rs, activate dopamine neurons indirectly through the OX1R-PLC-DAGL-2-AG-CB1R cascade in the VTA, leading to cocaine relapse.
[1]Tung et al. (2016) Orexins contribute to restraint stress-induced cocaine relapse by endocannabinoid-mediated disinhibition of dopaminergic neurons. *Nature Communications* 7:12199.

Disclosures: L. Chiou: None. **Y. Chou:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

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Program#/Poster#: 657.09/D21

Topic: B.03. G-Protein Coupled Receptors

Support: NIDA Intramural Funds

Ministerio de Economia y Competitividad SAF2014-54840-R

Fundacio La Marato de TV3 20140610

Government of Catalonia 2014-SGR-1236

Title: Functionally significant oligomers of ghrelin and dopamine D1-like receptors control dopaminergic cell activity in the VTA

Authors: *W. P. REA[1], C. QUIROZ[1], M. HEARING[2], G. NAVARRO[3], E. MORENO[3], A. CORTES[3], E. I. CANELA[3], V. CASADO[3], S. FERRE[1]

[1]Integrative Neurobio., NIDA/IRP/NIH, Baltimore, MD; [2]Marquette Univ., Milwaukee, WI; [3]Univ. of Barcelona, Barcelona, Spain

Abstract: The orexigenic hormone ghrelin acts on a G protein-coupled receptor known as growth hormone secretagogue (GHS) receptor or GHS-R1a. Cells expressing GHS-R1a also express GHS-R1b, a truncated isoform variant of GHS-R1a lacking the transmembrane domains 6 and 7. Ghrelin does not bind to and therefore does not signal through GHS-R1b. We recently showed that GHS-R1b determines the efficacy of ghrelin-induced GHS-R1a-mediated signaling and the ability of GHS-R1a to form oligomeric complexes with other receptors, including the dopamine D_1 receptor (D1R), promoting profound qualitative changes in ghrelin-induced signaling. Both in mammalian transfected cells and striatal neurons, the D_1-like receptor antagonist SCH-23390 counteracted GHS-R1a-mediated signaling by acting on GHS-R1a-GHS-R1b-D1R oligomers (cross-antagonism). The orexigenic effects of ghrelin are related to its ability to indirectly and directly activate dopamine cells of the VTA, through activation of GSH-R1a localized in neurons of the hypothalamic arcuate nucleus (hypothalamic-VTA connection) and in the somatodendritic region of the dopamine cells in the VTA. Since somatodendritic dopamine release in the VTA is a correlate of dopaminergic cell firing, its analysis can be used to study the local modulation of dopamine cell function. Our recently introduced "infusion-microdialysis probe" allows the slow and constant delivery of large peptides into the same brain region that is being sampled for extracellular concentrations of dopamine. Using this method, we obtained preliminary results showing a substantial increase in somatodendritic dopamine release with direct infusion of ghrelin in the VTA, which was completely blocked by co-perfusion (reverse dialysis) of SCH-23390, strongly suggesting that we identified a significant functional population of GHS-R1a-GHS-R1b-D1R oligomers in the VTA. Since the D_5 receptor (D5R) has been suggested to be the predominant D_1-like receptor in the VTA, we performed experiments in mammalian transfected cells to confirm that GHS-R1a, GHS-R1b and D5R can also from oligomers with the same biochemical properties than GHS-R1a-GHS-R1b-D1 oligomers, including the cross-antagonism. Finally, preliminary data using patch-clamp electrophysiological analysis of dopamine cell activity in the VTA shows that ghrelin does increase spontaneous firing. We intend to show that this effect is counteracted by SCH-23390 and that this cross-antagonism is disrupted by synthetic peptides that disrupt heteromerization, demonstrating the presence of functionally significant GHS-R1a-GHS-R1b-D_1-like receptor oligomers in the dopaminergic cells of the VTA.

Disclosures: W.P. Rea: None. **C. Quiroz:** None. **M. Hearing:** None. **G. Navarro:** None. **E. Moreno:** None. **A. Cortes:** None. **E.I. Canela:** None. **V. Casado:** None. **S. Ferre:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 657.10/D22

Topic: B.03. G-Protein Coupled Receptors

Title: Regulation of type 1 glucose transporter (glut-1) levels by histamine h1 and h3 receptors in rats astrocytes in primary cultures

Authors: *J. PARRA
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Abstract: Histamine acts as neurotransmitter and neuromodulator in the Central Nervous System and is involved in various functions such as sleep/wakefulness, hormonal secretion, thermoregulation, food intake, memory and glucose metabolism in neurons and glial cells. These effects are mediated by the activation of four G protein-coupled receptors (H_1R, H_2R, H_3R, and H_4R). Astrocytes take up and metabolize large amounts of glucose, and express the 45 kDa isoform of the type 1 glucose transporter (GLUT-1), involved in the bidirectional, facilitated transport of glucose. Astrocytes express H_1Rs and H_3Rs, which through $G\alpha_{q/11}$ and $G\alpha_{i/o}$ proteins, respectively, trigger several signaling pathways. In this work, we therefore set to study whether the activation of H_1Rs and H_3Rs regulates GLUT-1 protein expression in rat astrocytes in primary culture.
Cultures were prepared from the cerebral cortex of neonatal (2 to 7-day old) Wistar rats. Receptor levels were determined by the specific binding to cell membranes of [^{3}H]-mepyramine (H_1R) or [^{3}H]-N-α-methylhistamine (H_3R). H_1R signaling was evaluated by measuring changes in the intracellular concentration of Ca^{2+} ($[Ca^{2+}]_i$), and H_3R function by the inhibition of forskolin-induced cAMP accumulation. GLUT-1 protein expression was evaluated by immunodetection.
Cultured astrocytes expressed both H_1Rs (230 ± 22 fmol/mg of protein) and H_3Rs (77 ± 15 fmol/mg of protein) in their membranes. H_1R activation resulted in Ca^{2+} mobilization from intracellular stores, and H_3R activation inhibited cAMP accumulation. Immunoblot assays showed that incubation for 3 h with 30 μM 2-pyridylethylamine (PEA) or 1 μM immepip (selective H_1R and H_3R agonists, respectively) significantly increased GLUT-1 levels to 164.3% ± 9.9 and 143.2% ± 9.8 of control values, respectively.
These results suggest that H_1Rs and H_2Rs regulate GLUT-1 protein levels and thus glucose uptake by astrocytes.

Disclosures: J. Parra: None.

Poster

657. Peptide Receptors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 657.11/D23

Topic: B.03. G-Protein Coupled Receptors

Support: National Institute on Drug Abuse Awards R01 DA030529

Title: Mu opioid agonists differentially affect VTA neurons that project to either prelimbic or infralimbic cortices

Authors: *J. M. BRETON[1], H. L. FIELDS[2], E. B. MARGOLIS[2]
[1]Neurosci., Univ. of California Berkeley, Berkeley, CA; [2]Neurol., UCSF, San Francisco, CA

Abstract: The ventral tegmental area (VTA) is a central brain region that is necessary for the hedonic actions of mu opioid receptor agonists. The dopaminergic projection from the VTA to the medial prefrontal cortex (mPFC) has been implicated in both positive and negative hedonic states. Critically, two subregions of the mPFC appear to play different and often opposing roles in behavior: the infralimbic (IL) and the prelimbic (PL) cortices. The PL appears to promote learned fear and drug seeking behaviors, while the IL inhibits these behaviors. Such diversity in the behavioral action raises the possibility that the connectivity, physiological and/or pharmacological properties of the VTA neurons composing these two projections may differ. While it is well established that individual VTA neurons generally project to just one target region, whether PL and IL receive inputs from separate populations of VTA neurons is unknown. To test the hypothesis that different VTA neurons project to the IL and PL, we injected different retrograde tracers ipsilaterally into the PL and IL of rats, and examined the VTA for tracer colocalization. We also performed immunocytochemistry, staining for tyrosine hydroxylase (TH), a marker of dopaminergic neurons. Our findings show there are largely non-overlapping projections from the VTA to the PL and IL and that these projections differ in the percentage of dopaminergic neurons (50% to IL and 23% to PL). These projections also differ in their location; there is a greater percentage of PL projecting neurons in the ventral VTA and IL projecting neurons in the dorsal VTA. Furthermore, we found distinct opioid effects in VTA neurons projecting to PL and IL; the mu opioid receptor agonist [D-Ala^2, NMe-Phe^4, Gly-ol^5]-enkephalin (DAMGO) on average inhibited dopaminergic projections to PL (4/8 TH(+) neurons inhibited, 0/8 excited), but on average *excited* dopaminergic projection to IL (5/16 TH(+) neurons excited, 6/16 inhibited, mean change in V_m = +1.56 mV). On the other hand, many nondopaminergic (TH(-)) neurons in both projections were inhibited by DAMGO (PL: 8/8 inhibited, IL: 5/11 inhibited 1/11 excited).
Our findings demonstrate that projections from the VTA to the PL and IL are anatomically distinct, differ in the proportion that are dopaminergic and are differentially controlled by mu opioid receptor activation. These findings indicate that future studies of mPFC need to carefully differentiate between these two cortical subregions. Future studies will aim to determine whether these two VTA projections contribute differentially to opioid seeking and opioid reinforced behaviors.

Disclosures: **J.M. Breton:** None. **H.L. Fields:** None. **E.B. Margolis:** None.

Poster

657. Peptide Receptors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 657.12/D24

Topic: B.03. G-Protein Coupled Receptors

Title: G protein-coupled receptors for gastrin releasing peptide regulate EGFR and HER2 transactivation

Authors: *T. W. MOODY
Office the Director, CCR, NCI, Bethesda, MD

Abstract: The bombesin (BB) family of peptides includes gastrin releasing peptide (GRP), which regulates pruritus, and neuromedin B (NMB) which causes satiety and thyrotropin secretion (Jensen et al., Pharmacol Rev 2008; 60: 1). GRP as well as dopamine decarboxylase and neuron specific enolase are present in high concentrations in the neuroendocrine tumor small cell lung cancer (SCLC, Carney et al., Cancer Res 1985; 45: 2913). GRP stimulates SCLC proliferation, whereas the GRP receptor antagonist PD176252 inhibits proliferation (Moody et al., Peptides 2015; 72: 106). Because peptide GPCR regulate RTK transactivation, the effects of GRP were investigated on EGFR and HER2 tyrosine phosphorylation. Addition of GRP to human SCLC cell line NCI-H345 increased EGFR, HER2 and ERK tyrosine phosphorylation 4-, 3- and 2-fold, respectively. The increase in EGFR and HER2 transactivation caused by GRP was inhibited by PD176252, gefitinib (EGFR tyrosine kinase inhibitor), PP2 (Src inhibitor), GM6001 (matrix metalloprotease inhibitor) and TGF alpha monoclonal antibody. GRP addition to SCLC cells increased the secretion of TGFalpha (EGFR agonist) into the media, which was inhibited by GM6001. The results suggest that the GRP receptor regulates MMP activity and that the released TGFalpha binds to the EGFR causing the formation of EGFR homodimers and EGFR/HER2 heterodimers. Gefitinib or PD176252 inhibited whereas GRP increased SCLC colony formation. PD176252 and gefitinib strongly inhibited SCLC growth and EGFR transactivation. The results indicate that the GRPR regulates SCLC proliferation in an EGFR- and HER2-dependent manner.

Disclosures: T.W. Moody: None.

Poster

657. Peptide Receptors

Location: Halls A-C

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Topic: B.03. G-Protein Coupled Receptors

Support: NSF grants IOS-1353023 and IOS-1354567

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Cades Foundation

Title: Multiple receptors for allatostatin-C peptides in the lobster: Nervous system: A possible substrate for differential responses to a neuropeptide?

Authors: *P. S. DICKINSON[1], P. WALSH[1], J. J. HULL[2], S. PONG[1], A. W. PUPO[1], A. E. CHRISTIE[3]
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Abstract: Peptides and their receptors represent the largest and most diverse signaling systems in the nervous system. We have identified three allatostatin-C peptide isoforms in the nervous system of the American lobster, *Homarus americanus*. Interestingly, while perfusion of the lobster heart with each of the peptides usually results in a decrease in contraction frequency, each can elicit either a decrease or an increase in contraction amplitude. One hypothesis to explain these differential responses is the differential distribution of multiple AST-C receptors among individuals. Using transcriptomes from the lobster brain and eyestalks, we have identified four putative AST-C receptors, and have confirmed and/or determined the full-length sequences of these receptors using PCR. Using these sequences, we have C-terminally tagged receptors I, II, and IV with EGFP, and have expressed them in insect cell lines; the expression of receptor III is in progress. Receptors I and II are expressed at the cell surface, where they co-localize with TAMRA-labelled AST-C1, suggesting that both receptors bind the AST-C isoform. No evidence of binding was observed in non-transfected cells, indicating that binding is specific to the expressed receptor. Receptor IV, however, appears to remain within vesicles in the cytoplasm; this may result from issues with receptor trafficking due to the presence of the EGFP tag. We are currently using two techniques to determine the relative binding and activation efficiencies of these receptors to the three AST-C isoforms. First, we are using competitive inhibition assays to determine the ability of AST-C2 and AST-C3 to compete with the labeled AST-C1. Second, we have loaded the cells expressing the receptors with a calcium-sensitive dye, and are following the fluorescence triggered by calcium release when the cells are challenged with each of the three peptides. These experiments have confirmed that AST-C receptors I and II are activated by all three peptides; experiments are ongoing to determine the relative binding efficacy of each peptide. Preliminary PCR data suggest that receptors II and III are expressed in the cardiac ganglion; experiments are ongoing to confirm this distribution and to determine whether receptors I and IV are likewise present in the cardiac ganglion. Differential receptor expression and activation by the three peptides may provide an explanation for the differential responses of individuals to allatostatin-C.

Disclosures: **P.S. Dickinson:** None. **P. Walsh:** None. **J.J. Hull:** None. **S. Pong:** None. **A.W. Pupo:** None. **A.E. Christie:** None.

Poster

658. Postsynaptic Receptors and Scaffolds

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 658.01/D26

Topic: B.07. Synaptic Transmission

Support: NSF 1322302 to ED

Whitehall Foundation Research Grant to ED

UC Davis startup funds to DF

Title: Investigation of the role of SynDIG1 in synaptic transmission in the cerebellum

Authors: Y. IDEGUCHI[1], C. QUARSHIE[1], S. VADDADI[1], S. JUNG[1], E. PEREZ[1], E. DIAZ[2], E. G. ANTZOULATOS[1], *D. FIORAVANTE[1]
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Abstract: SynDIG1 (synapse differentiation induced gene 1) is a highly conserved membrane protein that regulates excitatory synapse number and synaptic strength by associating with AMPA receptors. Specifically, knockdown of SynDIG1 in dissociated hippocampal neurons decreases AMPA receptor content at synapses by approx. 50% (Kalashnikova et al. 2010). Disruption of SynDIG1 results in decreased number of mature synapses and average postsynaptic density (PSD) length in the CA1 region of the hippocampus (Chenaux et al. 2016). Increased short-term structural plasticity is also observed in SynDIG1-deficient mice upon glutamate stimulation of individual dendritic spines (Chenaux et al. 2016). Because SynDIG1 mRNA is upregulated during postnatal development in the cerebellum (Diaz et al. 2002), and in the cerebellum SynDIG1 protein is selectively expressed in Purkinje neurons (Chenaux et al. 2016), we sought to characterize the effects of SynDIG1 disruption on synaptic transmission and plasticity of cerebellar synapses, starting with the parallel fiber to Purkinje cell synapse. Acute cerebellar slices from postnatal day P8-P21 mice were prepared and whole cell voltage-clamp recordings were obtained from Purkinje cells in the presence of the sodium channel blocker TTX and the $GABA_A$ receptor antagonist bicuculline. Preliminary results suggest a decrease in mEPSC amplitude, but not frequency, in SynDIG1-deficient mice compared to wild type littermate controls. This effect, which was seen in slices from P8-P12 but not P18-P21 animals, agrees with the previously observed postsynaptic role of SynDIG1 in AMPA receptor regulation

in the hippocampus. We are currently investigating evoked glutamatergic transmission as well as climbing fiber territory and plasticity.

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Poster

658. Postsynaptic Receptors and Scaffolds

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 658.02/D27

Topic: B.08. Synaptic Plasticity

Support: Pinsent Darwin Scholarship

Title: Neuronal pentraxin 2 binds to the perineuronal nets via hyaluronan

Authors: *H. M. VAN 'T SPIJKER[1], J. C. KWOK[2], J. W. FAWCETT[1]
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Abstract: Introduction
Perineuronal nets (PNNs) are mesh-like structures which form at the end of the critical period for plasticity, in the extracellular matrix of sub-populations of neurons in the CNS. The PNNs consist of a backbone of hyaluronan (HA) which is linked to a variety of chondroitin sulfate glycosaminoglycans by link proteins. However, the mechanisms by which PNNs interact with synapses are poorly understood.
Materials & Methods
In this project, I aim to investigate a newly identified binding partner of PNNs, Neuronal Pentraxin 2 (NPTX2) and to determine the mechanism by which NPTX2 regulates interactions between PNNs and synapses using both molecular biology and microscopy methods. I applied both modified glycan ELISA and Quartz Crystal Microbalance with Disspation (QCM-D) to investigate the binding properties and I investigated the localization of NPTX2 with primary cortical neuronal cultures and fluorescence microscopy.
Results
With the use of modified glycan ELISA, we observed a strong binding of NPTX2 to HA and chondroitin sulphate E, but not to other PNN glycans. QCM-D investigation of the binding of NPTX2 and HA displayed the binding is reversible. In cultured neurons NPTX2 co-localizes with the PNN.
Discussion
Because NPTX2 has previously been reported as a binding partner for AMPA receptors and removal of PNNs also increase AMPA receptor mobility, our results indicate that PNNs may

control synaptic plasticity through the binding of NPTX2 which regulates the activity and signalling cascade of AMPA receptors. Further experiments are necessary to investigate the potential of NPTX2 as a mediator of the effects of the PNNs.

Disclosures: H.M. Van 't Spijker: None. **J.C. Kwok:** None. **J.W. Fawcett:** None.

Poster

658. Postsynaptic Receptors and Scaffolds

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Topic: B.07. Synaptic Transmission

Support: Wellcome Trust Grant HEALTH-F2-2009-241498

CIBERNED Grant CB06/05/0066

Title: The synaptome map of the whole mouse brain: A molecular template for the architecture of circuits and behavior

Authors: Z. QIU[1], F. ZHU[1], M. CIZERON[1], R. BENAVIDES-PICCIONE[2], M. KOPANITSA[3], N. SKENE[1], J. DEFELIPE[2], E. A. FRANSEN[4], N. KOMIYAMA[1], *S. G. GRANT[1]
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Abstract: The “synaptome” refers to the complement of all synapses in the brain, or part thereof, and to date no studies have mapped the molecular expression in single synapses across the whole brain of any vertebrate. To map the synaptome at the whole brain scale, we have developed a technology pipeline called “Genes to Cognition Synaptome Mapping Pipeline” (G2CSynMaP), which is a standardized image capture and analysis suite built for use with genetically engineered mice expressing tagged postsynaptic proteins. We systematically characterized and classified billions of individual synapses into 37 subtypes in mice based on synaptic molecular composition and physical parameters, and generated the first whole brain scale synaptome maps at the single synapse resolution. Synaptome maps revealed remarkable complexity with many hitherto unknown anatomical features including layers, patches and gradients of different subtypes of synapses. From single synapses on individual dendrites to the whole brain, striking and novel architecture were observed in the spatial diversity of synapse subtypes. The hippocampus showed highest synaptic diversity with gradients that localize neural activity patterns and encode behavioral representations. Long-range connections and mesoscale connectome architecture were also defined by synaptome maps. Mutations causing mental disorders reprogramed global synaptome architecture and reconfigured representations. The

complexity of synaptome maps expanded with vertebrate genome evolution. We propose that synaptome maps act as templates for the representation of behaviors in the brain. We predict that the brain's function may depends on a vast number of synaptome maps and that they will reveal many architectural and functional features at all scales. The whole brain synaptome mapping resources reported here can be expanded to include other synapse proteins, define new anatomical features and be integrated with other large-scale brain map resources. Synaptome technology can be used in a wide range of basic science and medical studies. It can also be used in conjunction with connectomic and optogenetic methods to address how the remarkable molecular and spatial diversity of synapses control the neural networks of the brain.

Disclosures: Z. Qiu: None. **F. Zhu:** None. **M. Cizeron:** None. **R. Benavides-Piccione:** None. **M. Kopanitsa:** None. **N. Skene:** None. **J. DeFelipe:** None. **E.A. Fransen:** None. **N. Komiyama:** None. **S.G. Grant:** None.

Poster

658. Postsynaptic Receptors and Scaffolds

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Topic: B.07. Synaptic Transmission

Support: NIH Grant 5F31MH105105

NIH Grant MH080046

The Kahlert Foundation

Title: Synaptic nanostructure is a novel regulator of NMDA receptor activation

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Abstract: Within a single synapse, there are several factors that may regulate NMDA-type glutamate receptor (NMDAR) response amplitude, including receptor number, subunit composition, and posttranslational modification. However, with the development of super-resolution imaging techniques we can now examine the question of how distribution of proteins within the synapse on a nanoscale level controls NMDAR activation. In order to measure NMDAR activation in individual synapses, we imaged the Ca^{2+} indicator GCaMP6f in cultured hippocampal neurons in the presence of TTX, 0 $Mg^{2+,}$ ryanodine, nifedipine and thapsigargin. This revealed miniature spontaneous NMDAR activation in individual dendritic spines, where the GCaMP6f response was sensitive to the total amount of NMDAR channel opening, because event amplitude could be modulated in either direction by altering the extracellular Mg^{2+} or Ca^{2+}

concentration.
Immunocytochemistry and focal glutamate delivery have suggested that tens of NMDARs are present at a single synapse. However, in our experiments, a low concentration of the high affinity antagonist CPP strongly decreased event frequency with a much smaller reduction in mean amplitude. This suggests that very few NMDARs open following spontaneous glutamate release. The low open probability of NMDARs after agonist binding likely contributes to this phenomenon, but, in addition, subsynaptic positioning of NMDARs away from release sites may minimize their activation. To examine the functional impact of subsynaptic NMDAR position, we used Monte Carlo simulations of model synapses created from measured super-resolution maps of NMDAR distribution. Simulating glutamate release at different positions within the active zone revealed that the open probability of NMDARs containing GluN2B but not GluN2A sharply decreased as a function of distance from the site of release (~50% in 80 nm). Surprisingly, in imaging experiments, the GluN2B antagonist eliminated the vast majority of spontaneous events. Thus, few NMDARs are activated during mEPSCs, but they are largely GluN2B-containing. To test the effect of synaptic nanostructure on NMDAR activation, we are combining super-resolution imaging of synaptic proteins with single-spine Ca^{2+} imaging. This revealed a positive correlation between NMDAR activation at single spines and the fractional area of the PSD that was incorporated into a nanodomain. Additionally, spines with prominent nanodomains showed a wider range of average peak amplitudes than spines that lacked nanodomains. Together, these data suggest PSD nanostructure is a novel mechanism for regulation of NMDAR activation.

Disclosures: **S. Ransom Metzbower:** None. **S. Raghavachari:** None. **T.A. Blanpied:** None.

Poster

658. Postsynaptic Receptors and Scaffolds

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Topic: B.07. Synaptic Transmission

Support: DFG SFB 1089

DI 852/7-1

DI 853/3-2

DI 853/5-1

SCHO 820/6-1

SCHO 820/5-2

Title: Spatial action range of glutamate

Authors: *D. DIETRICH, W. SUN, S. MCMAHON, E. A. MATTHEWS, A. J. MÜLLER, S. SCHOCH
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Abstract: Synaptic wiring of neurons is considered to be almost as specific as hard-wiring of electronic devices as potent uptake mechanisms are assumed to remove glutamate before it can activate AMPA receptors at neighboring spines. However, the neuropil ultrastructurally is very crowded such that the nearest neighbor synapse is found at ~300-500 nm but it has not yet been determined which distance glutamate molecules can travel in the extracellular space and activate AMPA receptors before being removed. Here we report that the action range of glutamate at AMPA receptors exceeds the distance to the nearest neighbor synapse in hippocampus predicting that quantal glutamate release regularly co-activate neighboring spines. We used two-photon glutamate uncaging and showed that the amplitude of spine-mediated AMPA receptor currents decline with a length constant of 440 nm (lambda). When blocking glutamate transporters, lambda increased to ~900 nm which also described the extracellular spread of two-photon activated dyes in hippocampus. Using neuronally expressed iGluSnfr we verified that our estimates of lambda based on glutamate uncaging closely match the spatial action range of single action potential-driven glutamate release from mossy fiber boutons. Monte Carlo simulations with a synaptic density of 2 μm^{-3} show that even at small fractions of activated synapses, cross-talk to AMPA receptors at neighboring spines contributes to ~20-30% of total synaptic currents in the input receiving network. The functional impact of this synaptic cross-talk is even enhanced because simultaneous spatially distributed glutamate uncaging events add in a supra-linear fashion at individual spines. Taken together, our data challenge the concept of point-to-point glutamatergic transmission and show that also the micron-scale spatial segregation of postsynaptic structures is a relevant parameter for network computation and excitability.

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Poster

658. Postsynaptic Receptors and Scaffolds

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: B.07. Synaptic Transmission

Support: NIH Grant NS085729

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Title: Differences between synaptically activated sodium concentration changes through AMPA and NMDA receptors in rat hippocampal pyramidal neuron dendritic spines

Authors: K. MIYAZAKI, *W. N. ROSS
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Abstract: Excitatory synaptic stimulation generates an epsp by activating AMPA and NMDA receptors on spines of pyramidal neurons. Factors that influence the relative contribution of these two receptors include (a) their relative affinity for glutamate, (b) the kinetics of their conductances, and (c) the effectiveness of the voltage-dependent Mg block of the NMDA receptors. We explored these factors and the role of sodium diffusion using simultaneous sodium and calcium imaging (Miyazaki and Ross, 2015) from dendritic spines.
Pyramidal neurons in hippocampal slices were patched and filled with bis-fura-2 (calcium) and ANG-2 (sodium). We selected dendrites near the surface where spines were often visible and positioned a stimulating electrode within 20 µm of a dendrite. Single or paired shocks at 10 ms separation often evoked localized (< 5 µm extent) fluorescence increases corresponding to sodium and calcium concentration changes. In most cases the sodium signal had a fast rise time of ~10 ms, which corresponds well with the rise time of the AMPA conductance. The rise time of the calcium signal was slower than the rise of the sodium signal, and well matched to the NMDA receptor-dependent calcium signal recorded by other investigators. CNQX blocked almost all of the sodium signal and most of the calcium signal. CPP blocked about 15% of the sodium signal and 90% of the calcium signal.
In seven cells we detected signals that clearly originated in single spines. The sodium signal rose sharply in the spine and then appeared later in the nearby dendrite. The calcium signal rose more slowly and was confined to the spine. These responses are consistent with strong buffering of calcium and free diffusion of sodium. The half removal time of the spine sodium signal was ~16 ms. A computer model assuming removal from the spine only by diffusion reproduced the sodium signals in the different compartments assuming spine and dendrite dimensions from the literature and measured value for the sodium diffusion constant. These time courses are consistent with a low spine neck resistance.
The rapid diffusion of sodium out the spine neck and the fast kinetics of the AMPA conductance helps to explain the apparent small contribution of NMDA receptor activation to the synaptic sodium signal. Removal by diffusion prevents the buildup of sodium during the slow activation of the NMDA receptor. In addition, the Mg block of the receptor is only relieved during the short (~7 ms) epsp in the spine, limiting the duration of sodium influx.

Disclosures: K. Miyazaki: None. **W.N. Ross:** None.

Poster

658. Postsynaptic Receptors and Scaffolds

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Title: Postsynaptic RIM1 modulates synaptic function by facilitating membrane delivery of recycling NMDARs in hippocampal neurons

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Abstract: NMDA receptors (NMDARs) are crucial for excitatory synaptic transmission and synaptic plasticity. The number and subunit composition of synaptic NMDARs are tightly controlled by neuronal activity and sensory experience, whereas the molecular mechanism mediating NMDAR trafficking remains poorly understood. Here we report that RIM1α, with a well-established role in presynaptic vesicle release, also localizes postsynaptically in the mouse hippocampus. Postsynaptic RIM1α in hippocampal CA1 region is required for basal NMDAR-, but not AMPA receptor (AMPAR)-, mediated synaptic responses, along with contributions to hippocampus-dependent memory. Moreover, RIM1α levels in hippocampal neurons determine both the constitutive and regulated NMDAR trafficking, with no role in constitutive AMPAR trafficking. We further demonstrate that RIM1α binds to Rab11 and disruption of their interaction or knockdown of RIM1α impairs membrane insertion of Rab11-positive recycling endosomes containing NMDARs. Together, these results identify a novel RIM1α-dependent mechanism critical for modulating synaptic function by facilitating membrane delivery of recycling NMDARs.

Disclosures: **X. Lv:** None. **J. Wang:** None. **J. Luo:** None. **S. Qiu:** None.

Poster

658. Postsynaptic Receptors and Scaffolds

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Topic: B.07. Synaptic Transmission

Support: NIH Grant NS080967

Brain Research Foundation BRFSG-2014-13

Title: Essential role for Parkin in AMPA and NMDA receptor trafficking and signaling

Authors: M. ZHU[1], G. P. CORTESE[2], *C. WAITES[3]
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Abstract: The PARK2 gene, encoding the E3 ubiquitin ligase Parkin, was originally discovered as a cause of early-onset Parkinson's disease and has been extensively studied in the context of dopaminergic neuron survival. However, Parkin is highly expressed throughout the brain and is a known component of the postsynaptic density at glutamatergic neurons. Recent genome-wide association studies have identified copy number variations in PARK2 that are linked to autism, developmental delay, ADHD, and intellectual disability, suggesting an essential role for Parkin in synaptic transmission and plasticity. Here, we investigate Parkin's role at glutamatergic synapses of the hippocampus, and find that Parkin deficiency leads to significantly decreased AMPA and NMDA receptor-mediated currents and cell-surface expression. Remarkably, our studies indicate that Parkin regulates the trafficking of each receptor type via a distinct mechanism: AMPA receptors through a structural role at the postsynaptic density, and NMDA receptors through direct ubiquitination. Moreover, we find that the trafficking defects induced by Parkin loss-of-function lead to impaired synaptic plasticity. Our findings demonstrate novel roles for Parkin in regulating synaptic glutamate receptor trafficking, and suggest a mechanism through which PARK2 copy number variations cause dysfunction of excitatory synaptic transmission and plasticity, leading to cognitive deficits associated with autism and intellectual disability.
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Poster

658. Postsynaptic Receptors and Scaffolds

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Title: Synaptotagmin 1 and SNARE proteins in postsynaptic spines: Regulation of AMPA receptor exocytosis

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Abstract: The last 25 years we have known that the core SNARE complex of VAMP2 (synaptobrevin 2), syntaxin 1 and SNAP-25 are crucial in facilitating and regulating presynaptic vesicular release. However, indirect evidence has also supported a postsynaptic role for SNARE proteins. The necessary postsynaptic vesicles were for a long time only implicated. Using postembedding immunogold electron microscopy in combination with biochemical techniques, we have demonstrated the presence of small vesicles in postsynaptic spines in the rat hippocampus. SNARE proteins and the Ca^{2+}-sensor synaptotagmin 1 are present on vesicular and plasma membranes in these spines. We find evidence that they are involved with exocytosis of glutamate receptor subunits.
In the current project, we show that **synaptotagmin 1** is present both on cytoplasmic vesicles, and at the postsynaptic density (PSD) and lateral membranes. In cytoplasmic compartments, the highest concentrations of synaptotagmin 1 are found in presynaptic terminals, almost 40 % higher than in postsynaptic spines. However, these spines show about 65 % higher concentrations than the corresponding dendritic shafts, and astrocytic processes showing only background levels of synaptotagmin 1. Less difference is found on cytoplasmic membranes, though also here presynaptic membrane (active zone) is clearly higher than the PSD, which is higher than dentritic membranes. We further investigated whether postsynaptic synaptotagmin 1 is regulated during synaptic plasticity. In a rat model of chronic temporal lobe epilepsy, we found that pre- and postsynaptic concentrations of the protein are reduced compared to control animals. This down regulation may be an adaptive measure to decrease both pre- and postsynaptic calcium sensitivity in excitotoxic conditions. Thus, postsynaptic AMPA receptor

concentrations are reduced correspondingly in the epilepsy model.
Similar to synaptotagmin 1, the SNARE proteins **syntaxin-1, SNAP-25** and **VAMP2** (synaptobrevin 2) are present in the highest concentrations at presynaptic compartments, including the active zone, supporting their role in neurotransmitter release. However, also these SNARE proteins are expressed at significant levels in postsynaptic spines. As we have reported previously, VAMP2 colocalizes with the AMPA receptor subunit GluA1 on the same postsynaptic vesicles. Disrupting VAMP2 by tetanus toxin treatment reduces the concentration of GluA1 in the postsynaptic plasma membrane, indicating that small postsynaptic vesicles containing GluA1 are inserted directly into the spine plasma membrane through a VAMP2-dependent mechanism.

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Poster

658. Postsynaptic Receptors and Scaffolds

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Title: Alpha-actinin anchors PSD-95 and AMPA receptors at postsynaptic sites

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St. Louis, MO; [7]Envrn. Engin., Akdeniz Univ., Antalya, Turkey; [8]Chem., Univ. of California, Davis, CA

Abstract: Despite the central role PSD-95 plays in anchoring postsynaptic AMPARs, how PSD-95 itself is tethered to postsynaptic sites remained unknown. Here we show that the F-actin binding protein α-actinin binds to the very N-terminus of PSD-95. Knock-down (kd) of α-actinin phenocopies kd of PSD-95. Mutating lysine at position 10 or lysine at position 11 of PSD-95 to glutamate impairs in parallel PSD-95 binding to α-actinin and postsynaptic localization of PSD-95 and AMPARs. Also, expression of mutant α-actinin which cannot interact with PSD-95 showed similar phenotype. These experiments unequivocally identify α-actinin as a critical PSD-95 anchor tethering the AMPAR - PSD-95 complex to postsynaptic sites.

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Poster

658. Postsynaptic Receptors and Scaffolds

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Title: PSD lattice structure and scaffold-adaptor protein model for PSD structure

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Abstract: Postsynaptic density (PSD) is a dynamic structure, which is localized immediately underneath the postsynaptic membrane and works an essential devise for synaptic transmission and synaptic plasticity. A well-known model for architecture of PSD of type I excitatory synapse comprises of several scaffolding proteins including shank, PSD-95, GKAP and homer, to which various molecules involved in postsynaptic signaling are associated (scaffold/adaptor protein

model). On the contrary, "PSD lattice" has been identified in the preparation obtained after treatment of synaptosome, SPM or Triton X-100-PSD with deoxycholate, a relatively strong detergent, and has been considered to be a basic backbone of type I PSDs before the proposal of scaffold/adaptor protein model. However, major constituents of the PSD lattice and the relationship between the PSD lattice and the scaffold/adaptor protein model have not been known. It is essential to know the details of molecular architecture of PSD for full understanding the mechanisms, at the molecular level, of dynamic nature of PSD, one of basis of synaptic plasticity. We purified a fraction enriched with PSD lattice-like structures. The structure was recovered in the fraction slightly lighter than the pellet that contained PSDs. The lattice-like structure was planar, of which diameter was similar to PSD, sparser than PSD, and contained mesh-like woven fibers when observed in thin-section electron micrograph. Components of the structure were examined by Western blotting, immuno-dot blotting and immuno-gold negative staining electron microscopy. This study will give a new insight on the molecular architecture of type I excitatory PSD and new architecture model will be discussed.

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Poster

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Support: NIH Grant R01-MH63232

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Title: Direct interaction between postsynaptic proteins Shank3 and CaMKII

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Abstract: Shank3 is a postsynaptic scaffolding protein that is important for organizing neurotransmitter receptor signaling complexes at excitatory synapses. Mutations or deletions in the *SHANK3* gene are associated with neuropsychiatric disorders, such as autism spectrum disorder (ASD) and schizophrenia. Shank3 contains several protein-protein interaction domains that link postsynaptic receptors to downstream signaling proteins and the actin cytoskeleton. Calcium/calmodulin-dependent protein kinase II (CaMKII) is a signaling protein that is activated by calcium influx through these postsynaptic receptors. Recent proteomics data from our lab found that Shank3 is overly abundant in CaMKII complexes in the postsynaptic density. Therefore, we hypothesized that CaMKII can directly bind to Shank3.

Here, we confirm that complexes containing Shank3 and CaMKII can be co-immunoprecipitated from mouse forebrain and co-transfected HEK293 cells. Using GST-pulldown and purified CaMKII, we have identified a minimal CaMKII-binding domain on Shank3. This direct interaction *in vitro* requires pre-activation of CaMKII by Thr286 autophosphorylation. We used site-directed mutagenesis to identify residues in Shank3 that are critical for the direct Shank3-CaMKII interaction *in vitro*, as well as the co-immunoprecipitation from transfected HEK293 cells, but not for Shank3 binding to other proteins, such as $Ca_V1.3$. Moreover, co-immunoprecipitation from transfected HEK293 cells is essentially abrogated by mutation of the Thr286 autophosphorylation site to phospho-null Alanine. Ongoing studies are testing the effects of disrupting the Shank3-CaMKII interaction on Shank3/CaMKII localization and neuronal morphology. Together, our data demonstrate that the synaptic scaffolding protein Shank3 contains a novel binding domain for activated CaMKII.

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Poster

658. Postsynaptic Receptors and Scaffolds

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Title: Severe impaired synaptic transmission in the Shank1/Shank3 double knock out mouse

Authors: *C. SALA[1], A. MOSSA[1], L. PONZONI[2], A. TOZZI[3], M. SALA[1], P. CALABRESI[3], T. M. BOECKERS[4], *C. SALA[1], C. VERPELLI[1]
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Abstract: Shank family proteins (Shank1, Shank2 and Shank3) are large scaffold proteins located at the excitatory glutamatergic synapses. They are essential for building the structure of dendritic spines as their expression is sufficient to drive spine formation and enlargement. Importantly Shank proteins are differentially expressed in brain areas critical for learning and cognition. In particular, Shank1 and Shank3 are both highly expressed in hippocampus and cortex. Since Shank proteins play a crucial role in synaptic formation and function, it is not surprising that deletions and mutations in *SHANK* family genes are strongly associated with neurodevelopmental and neuropsychiatric disorders such as autism spectrum disorders (ASD)

and intellectual disability (ID). To dissect the role of these proteins in synapse function, we generated the Shank1/Shank3 double knock out (DKO) mouse. We found that Shank1/Shank3 deletion strongly reduce mice survival with a pick of mortality at P22-25. We then started to analyze young (P23) Shank1/3 DKO mice. PSD enriched fractions obtained from cortex show that the absence of Shank1 and Shank3 proteins cause a significant reduction of mGlu5 and Homer expression as well as reduced phosphorylation of eEF2, Akt, S6, Erk1/2 and Arc, suggesting that absence of Shank1 and Shank3 causes a functional reduction of the pathway that control protein translation. Moreover, we found that in both cortex and hippocampus of Shank1/3 DKO mice neurons exhibit reduced dendritic arborization and a reduced size of PSD. To clarify how these alterations affect brain functions we performed a battery of behavioral tests revealing that the Shank1/3 DKO mice have strong impairments in cognitive properties, social approach, repetitive behaviors and motor functions. These behavioral alterations are associated with an increase of cortical spikes measured by EEG recording and alterations in hippocampal LTP specifically in CA3. In summary, our results demonstrate the essential role of Shank1 and Shank3 in regulating hippocampal and cortical synapse maturation and function.

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Poster

658. Postsynaptic Receptors and Scaffolds

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Topic: B.07. Synaptic Transmission

Title: Kalirin interacts with neuroligin family members as revealed by unbiased screens from brain and *In situ* analyses

Authors: *J. PASKUS[1], M. BEMBEN[2], Y. LI[1], K. W. ROCHE[1]
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Abstract: Alterations in dendritic spine morphology and function are critical for the synaptic plasticity underlying learning and memory. The Rho guanine nucleotide exchange factor Kalirin has been implicated as an important mediator of many processes including synaptic transmission and plasticity. The single Kalirin gene is alternatively spliced, resulting in multiple isoforms; however, Kalirin-7 is the only brain specific protein variant. Kalirin has multiple binding partners that have been reported, though the mechanism by which Kalirin-7 regulates synaptic transmission, particularly which protein-protein interactions are significant, remains largely unclear. To study Kalirin-7 protein interactions we first generated a Kalirin-7 specific antibody. Immunoprecipitating endogenous Kalirin-7 from mouse brain, we used liquid chromatography-tandem mass spectrometry to screen for potential Kalirin-7 interactors. Of potential hits,

members of the Neuroligin (NLGN) family of cell adhesion proteins were of particular interest given their overlapping phenotype with Kalirin-7, namely their ability to regulate spinogenesis. To test whether Kalirin-7 and NLGNs could interact, we performed co-immunoprecipitation experiments both *in vitro* and *in vivo*. Our results demonstrated that Kalirin-7 can interact with NLGN1, 2 and 3. Given high sequence conservation between Kalirin isoforms, we then tested whether other major Kalirin isoforms (5, 9, and 12) could interact with NLGN1 as well. Surprisingly, Kalirin-5 was not able to interact with NLGN1 *in vitro*, suggesting NLGNs interact with the N-terminal domains of Kalirin-7, 9, and 12, which are lacking in 5. Interestingly, Kalirin-7 and 5 both contain a PDZ-interacting motif, that appears not to mediate the interaction with NLGNs. Taken together, we demonstrate that NLGNs can interact with Kalirin-7, but not with all Kalirin isoforms. These data establish a novel isoform-specific interaction between two major proteins of the postsynaptic density.

Disclosures: J. Paskus: None. **M. Bemben:** None. **Y. Li:** None. **K.W. Roche:** None.

Poster

658. Postsynaptic Receptors and Scaffolds

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Topic: B.07. Synaptic Transmission

Title: Identification of a novel PKA regulatory site in neuroligin-1

Authors: *J. JEONG[1], M. A. BEMBEN[1,2], Y. LI[1], K. W. ROCHE[1]
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Abstract: Neuroligin-1 is a member of the neuroligin gene family encoding a single-pass transmembrane postsynaptic cell adhesion molecule that is critical for excitatory synaptic assembly and function. The large extracellular domain of neuroligin-1 is responsible for transsynaptic binding with neurexin, a presynaptic cell adhesion molecule, and the short cytoplasmic tail of neuroligin-1 is exposed to a variety of intracellular regulation. Importantly, neuroligin-1 binds to PSD-95, a scaffolding protein at excitatory synapses, through the PDZ ligand in the cytoplasmic tail, which is important for neuroligin-1 clustering at excitatory synapses.
In this study, we found protein kinase A (PKA) phosphorylates neuroligin-1, near the PDZ ligand, *in vitro* and in heterologous cells. Interestingly, a phospho-mimetic mutation at the PKA site significantly reduced the interaction between neuroligin-1 and PSD-95 *in vitro* and *in situ*. The phospho-mimetic mutant also showed reduced surface expression levels in cultured neurons, which implies an effect of the phosphorylation in neuroligin-1 trafficking and further functional consequences in neurons. Our results establish a novel molecular mechanism that regulates

neuroligin-1 and PSD-95 binding in a PKA activity-dependent manner, which can provide insights into excitatory synaptic development and function.

Disclosures: **J. Jeong:** A. Employment/Salary (full or part-time):; NIH. **M.A. Bemben:** None. **Y. Li:** A. Employment/Salary (full or part-time):; NIH. **K.W. Roche:** A. Employment/Salary (full or part-time):; NIH.

Poster

658. Postsynaptic Receptors and Scaffolds

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Title: AMPA receptor stabilization mediated by non-canonical Wnt signaling protects synapses against $A\beta_{42}$ oligomers synaptotoxicity

Authors: *C. MONTECINOS OLIVA[1,2,3], D. CHOQUET[2,3], N. INESTROSA[4]
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Abstract: AMPA receptors are responsible for most of fast excitatory transmission in hippocampal neurons. They are among the most dynamic glutamate receptors. The mechanisms surrounding the organization of AMPA receptors are being elucidated. Wnt5a, a non-canonical Wnt ligand, is a morphogen acting in the maintenance of dendritic arborization on hippocampal neurons. Wnt5a has been linked to several roles in mature hippocampal neurons; dendritic spine density, number of PSD95 clusters and glutamatergic currents that are tuned by Wnt5a in hippocampal neurons in culture. This leads to suggest a key role of Wnt5a in the architecture of excitatory synapses. Glutamatergic synapses are affected by $A\beta_{42}$ oligomers causing AMPA receptor endocytosis, diminished dendritic spine density and causing overall failures in synaptic excitatory transmission; effects being englobed in the term "Aβ oligomers synaptotoxicity". On the contrary, it has been shown that Wnt5a protects neurons against $A\beta_{42}$ oligomers synaptotoxicity. Given the fact that Wnt5a seems to counteract the distresses caused by $A\beta_{42}$

oligomers. We studied the mechanism through which Wnt5a protects from $A\beta_{42}$ oligomers. This led us to evaluate the effect of Wnt5a on AMPA receptor dynamic. By using super-resolution microscopy in live and fixed hippocampal neurons (14-16 DIV), we found that Wnt5a modulates the dynamic and localization of AMPA receptors. Specifically, Wnt5a immobilizes AMPA receptors in synaptic and extrasynaptic sites. This correlates with an increase in co-localization and interaction between GluA2 and PSD95 in dendritic spines, as measured by immunofluorescence and co-immunoprecipitation. These effects are exerted only by non-canonical activation, through Wnt5a ligand and not by the canonical effects of Wnt7a. Interestingly, pre-incubation of Wnt5a prevents toxicity of $A\beta_{42}$ oligomers and maintains basal AMPA receptors dynamics.
Our data suggests that Wnt5a prevents $A\beta_{42}$ oligomers effects by immobilizing AMPA receptors in synaptic and extrasynaptic sites.

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Poster

658. Postsynaptic Receptors and Scaffolds

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Title: Removal of a genomic mutation in an actin motor protein by DN-CRISPRs reverts hyper-excitability and anxiety behavior in Flailer mice

Authors: *F. J. BUSTOS[1], S. PANDIAN[1], J.-P. ZHAO[1], M. HEIDENREICH[1], H. STROUF[1], F. ZHANG[1,2], M. CONSTANTINE-PATON[1]
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Abstract: Myosin Va (MyoVa) is a dimer and + end actin motor. Flailer *(*Flr*)* mice express 2 copies of a mutant *myo5a* driven by the brain-specific promoter for *gnb5* fused in frame with a *myo5a* sequence lacking DNA encoding the distal lever arm and the ATP hydrolyzing end-feet of the motor. Mutant MyoVa thus binds cargo, but cannot perform its CNS function of moving post-synaptic molecules to the PSD on excitatory neuron spines. Both WT GnB5 and WT

MyoVa are intact in these mice. However, when Flr is homozygous for the *flr* gene the transport of WT smooth ER into spines is disrupted (Jones et al., 2000), synaptic molecules are largely restricted to dendritic shafts, and NMDAR LTD is missing (Yoshi et al., 2013). Whole body mutations of *myo5a* cause early death in rodents (Mercer et al., 1991) and humans, (Griscelli et al., 1978 and Elejalde et al., 1979) but mice homozygous for the *flr* gene, despite abnormal behaviors, live and breed normally. Removing the *flr* gene from specific brain regions would allow analyses of the pathways involved in the abnormal behaviors of *Flailer* mice. Double-nicking CRISPRs were targeted to the *flr* genomic sequence to remove a fragment of the *flr* gene without altering the endogenous DNA sequences of either *myo5a* or *gnb5*. This deletion produced a significant decrease in both *flr* mRNA and protein levels in *Flailer* neurons without altering expression levels of WT Gnb5 or MyoVa. Immunofluorescence experiments using antibodies against PSD95 and Synaptophysin demonstrate that clustering of synaptic proteins is recovered in neurons. Whole cell patch clamp recordings showed that hyper-excitability displayed by Flailer neurons was reverted to WT levels after infection with CRISPRs. Finally, viral stereotaxic introduction of these CRISPRs into ventral hippocampus reverted one of the anxiety phenotypes displayed by the Flailer.
Work supported by: The McGovern Institute for Brain Research at MIT, NIH RO1EY14074, Pew and a Simons Postdoctoral Fellowships to FJB.

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Poster

658. Postsynaptic Receptors and Scaffolds

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 658.18/D43

Topic: B.07. Synaptic Transmission

Support: Telethon GGP11043 to Andrea Barberis

Title: Spectroscopy approaches for the study of inhibitory post-synaptic proteins during plasticity

Authors: *F. COLACI[1], L. SCIPIONI[2], A. DIASPRO[2], P. BIANCHINI[2], L. LANZANÒ[2], A. BARBERIS[1]
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Abstract: The fast diffusion of synaptic proteins has been shown to play an important role in the activity-dependent shaping of the synaptic strength. Our previous work demonstrated that during inhibitory long term potentiation (iLTP) gephyrin and GABAA receptors are accumulated at post-synaptic inhibitory sites. However, the events modulate the interactions between scaffold proteins and neurotransmitter receptors are poorly understood. To investigate the coordinated diffusion dynamics of the main GABAergic post synaptic proteins gephyrin and GABAA receptors we used Fluorescence Correlation Spectroscopy (FCS) and Raster Image Correlation Spectroscopy (RICS) to study the mobility of fluorescent proteins in both the plasma membrane and the cytoplasmic space. Our data suggest that, similarly to GABAA receptors, gephyrin molecules freely diffuse in the extrasynaptic space and are immobilized at both synaptic and extrasynaptic clusters in mice hippocampal cultured neurons. This spectroscopy approach allowed characterizing the mechanisms of synaptic clustering in basal conditions and during synaptic plasticity at inhibitory synapses.

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Poster

658. Postsynaptic Receptors and Scaffolds

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Topic: B.07. Synaptic Transmission

Support: MOST 103-2325-B-039-006 from the National Science Council, Taiwan

Title: Free radical scavenger edaravone attenuates oxidative stress-induced gephyrin cleavage in developing neurons and neonatal hypoxia

Authors: *C.-C. HUNG[1], C.-Y. LEE[1], W.-H. CHIEN[1], C.-H. LIN[4], Y.-L. GAN[1], C.-J. JENG[2,3], C.-Y. WANG[1], Y.-H. LEE[1,3]
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Abstract: Gephyrin is the postsynaptic scaffolding protein for clustering $GABA_A$ receptors ($GABA_AR$) at inhibitory synapses. Our previous report indicated that gephyrin aggregation is regulated by growth-associated protein 43 (GAP43), an activity-dependent neuroplasticity protein, in developing cortical neurons. The growth-promoting activity of GAP43 depends on the PKC-dependent phosphorylation at serine 41 (S41) to stabilize actin filaments. We have shown that both in vitro and in vivo models of neonatal hypoxic-ischemic (HI) brain injury can increase GAP43-gephyrin association and decrease cell surface $GABA_AR$ via dephosphorylation of GAP43 at Ser41. The production of oxidative stress was found in neonatal HI brain injury. Here

we examined the effect of oxidative stress on the gephyrin clustering by using H_2O_2 and buthioninesulfoximine (BSO), a glutathione (GSH) synthase inhibitor to reduce the endogenous antioxidant glutathione. We found that both oxidative stress inducers moderately dephosphorylated GAP43 and yet markedly promoted gephyrin cleavage, but not misfolding, in developing rat cortical neurons. The BSO-induced gephyrin cleavage was calpain-dependent as it was blocked by calpain inhibitors calpeptin, MDL28170 and ALLN in both cultured neurons and mCherry-gephyrin-transfected HEK293T cells. However, co-immunoprecipitation result showed that BSO did not increase the association of GAP43 with either full-length or cleaved gephyrin. Treatment with edaravone, a clinically used free radical scavenger, to primary cortical neurons attenuated BSO-induced GAP43 dephosphorylation and gephyrin cleavage. In a transient HI-induced neonatal rat brain injury, both GAP43 dephosphorylation and gephyrin cleavage were increased at the ipsilateral cortex, and these detrimental effects were attenuated by intraperitoneal injection of edaravone. Immunofluorescent staining further revealed that tHI increased both gephyrin clusters as well as non-gephyrin misfolded protein signals in CA3 pyramidal neurons. Edaravone treatment profoundly reduced tHI-induced misfolded protein signals without reducing the tHI-increased gephyrin clusters, which represent GABAergic synapses. In summary, our data suggest that oxidative stress induces GAP43 dephosphorylation and calpain-dependent gephyrin cleavage in developing cortical neurons. Edaravone treatment may provide beneficial effect by attenuating these detrimental effects in neonatal brain injury.

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Poster

658. Postsynaptic Receptors and Scaffolds

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Topic: B.07. Synaptic Transmission

Support: Genetics Training Program Fellowship T32GM007544

Title: A rare variant in ANK3 in a patient with bipolar disorder leads to altered GABAergic inhibitory circuits

Authors: *A. D. NELSON[1,2], R. N. CABALLERO-FLORÁN[2], K. K. WALDER[4], V. BENNETT[5], P. M. JENKINS[3]
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Abstract: Bipolar disorder is a common mental illness characterized by pathological swings in mood ranging from mania to depression. Available therapeutics are insufficient for effectively treating the underlying cause of bipolar disorder, thus there is an unmet need to identify the cellular mechanisms that contribute to bipolar disorder to identify new therapeutic targets. Several large genome-wide association studies have identified *ANK3* as one of the most consistent and significant genes associated with bipolar disorder. The giant, 480kDa splice variant ankyrin-G (product of the *ANK3* gene) is a critical adaptor protein essential for the proper formation of axon initial segments and nodes of Ranvier. Recently, giant ankyrin-G was discovered to be critical for stabilizing GABAergic inhibitory synapses, which underlie the proper synchronization and function of neuronal networks, and abnormalities in GABAergic interneuron circuitry have been linked to bipolar disorder. Using cultured neurons, we have shown that giant ankyrin-G interacts directly with GABA receptor associated protein (GABARAP) to inhibit $GABA_A$ receptor endocytosis and stabilize GABAergic synapses. To test this mechanism *in vivo*, we generated a mouse model with a W1989R mutation in *Ank3*, which completely abolishes ankyrin-G association with GABARAP, as well as $GABA_A$ receptor clustering *in vitro.* Coronal brain sections from *Ank3* W1989R mice showed the loss of GABAergic basket cell synapses on cortical pyramidal neurons in layer II/III of the somatosensory cortex. In addition, whole-cell patch clamp recordings of miniature inhibitory postsynaptic currents (mIPSCs) revealed a reduction in both the frequency and amplitude of inhibitory $GABA_A$ receptor-dependent currents. The axon initial segments and nodes of Ranvier are spared in the W1989R mouse, making this a useful model to study the specific role of ankyrin-G and GABAergic circuitry to understand how dysfunction in these circuits may contribute to neuropsychiatric disease. Interestingly, we identified a lithium-responsive individual with bipolar disorder type I who is heterozygous for the W1989R mutation within the giant exon of *ANK3*. Future studies will examine neurons derived from induced pluripotent stem cells (iPCSs) from the W1989R *ANK3* patient and neurotypical controls to evaluate GABAergic signaling and the ability of potential therapeutics, particularly lithium, to rescue abnormal electrophysiology. Ultimately, establishing the mechanisms by which giant ankyrin-G regulates GABAergic circuitry may reveal novel therapeutic targets for the treatment of neuropsychiatric disorders.

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Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Support: NIH Grant DA039533

Title: A novel role for corticotropin releasing factor signaling in the lateral habenula and its modulation by early life stress

Authors: *M. E. AUTHEMENT[1], R. D. SHEPARD[2], L. D. LANGLOIS[3], F. S. NUGENT[1]
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Abstract: Centrally released corticotropin releasing factor (i.e., extrahypothalamic CRF) acting within various brain regions is involved in behavioral and emotional responses to stress. Here, we demonstrate for the first time that extrahypothalamic CRF neurotransmission exists in the lateral habenula (LHb), an epithalamic brain region involved in stress evasion. Dysfunction of the CRF system and LHb is critical for development of stress-related disorders and addiction, however no study has investigated whether CRF signaling plays a role in activity of the LHb. In fact, the LHb shows immunoreactivity for both CRF and its receptor, CRFR1, and receives inputs from the structures that comprise the extrahypothalamic CRF system, but its involvement in this central CRF system is unexplored. Using whole cell patch clamp recording from rat LHb neurons, we found that CRF-CRF receptor 1(CRFR1) signaling increases the intrinsic excitability of LHb neurons through modulation of small- and large-conductance SK- and BK-type K^+ channels. In addition CRF reduced GABAergic synaptic transmission onto LHb neuron promoting LHb hyperactivity. Maternal deprivation (MD), a severe early life stress known to predict later-life psychiatric disorders, increases LHb neuronal excitability and blunts the excitatory actions of CRF on LHb neurons due to down-regulation of SK2 channel expression. Increasing the function of SK channels by positive allosteric modulation not only prevents CRF excitatory action on LHb intrinsic excitability but also reverses the effects of MD on LHb intrinsic excitability suggesting that SK channels may serve as novel pharmacological target in reversal of dysregulated stress-responsivity within the LHb during severe early life stress.

Disclosures: M.E. Authement: None. **R.D. Shepard:** None. **L.D. Langlois:** None. **F.S. Nugent:** None.

Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Support: Vanier Scholarship 338319

CIHR MOP-25953

Title: Neuropeptide modulation of CeA to ovBNST inhibitory inputs

Authors: *C. P. NORMANDEAU[1], M. L. TORRUELLA-SUAREZ[2], Z. A. MCELLIGOTT[3], E. C. DUMONT[1]
[1]Biol., Queen's Univ., Kingston, ON, Canada; [2]Univ. of North Carolina, Chapel Hill, NC; [3]Univ. of North Carolina, Chapel Hill, Chapel Hill, NC

Abstract: Neuropeptides have been targets of therapy in the past, but to no avail, possibly due to our lack of understanding of their physiological role in the brain. In a previous study, we found that locally synthesized and released neurotensin is a significant contributor to chronic stress-induced inhibitory transmission changes in the oval Bed Nucleus of the Stria Terminalis (BNST) and promote anxiety-like behaviours in rats. Here, we combined, optogenetic neurophysiology and fluorescent *in situ* hybridization imaging to better understand the neurocircuitry affected by local neuropeptides release in this brain region. We show that neurotensin and dynorphin bi-directionally regulated central amygdala inhibitory inputs onto ovBNST neurons in the mouse. In sum, our data expands our understanding of neuropeptidergic neuromodulation within extended amygdala circuits.

Disclosures: C.P. Normandeau: None. **M.L. Torruella-Suarez:** None. **Z.A. McElligott:** None. **E.C. Dumont:** None.

Poster

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ERC-2013-CoG NeuroMolAnatomy

Sagol School of Neuroscience

Title: IGF-1 receptor differentially regulates spontaneous and evoked transmission via mitochondria at hippocampal synapses

Authors: *N. GAZIT[1], I. VERTKIN[1], I. SHAPIRA[1], M. HELM[2], E. SLOMOWITZ[1], M. SHEIBA[1], Y. MOR[1], S. RIZZOLI[2], I. SLUTSKY[1]
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Abstract: The insulin-like growth factor-1 receptor (IGF-1R) signaling is a key regulator of lifespan, growth, and development. While reduced IGF-1R signaling delays aging and Alzheimer's disease (AD) progression, whether and how it regulates information processing at central synapses remains elusive. In this study we aimed to identify the role of IGF-1Rs in normal synaptic function, characterize cellular and molecular mechanisms underlying IGF-1R-mediated synaptic modifications and determine whether IGF-1R signaling impacts early synaptic dysfunctions in AD model mice. To answer these questions, we combined fluorescence resonance energy transfer (FRET) spectroscopy, FM-based optical imaging of synaptic vesicles, cytosolic and mitochondrial Ca^{2+} imaging, electrophysiology and biochemistry. We show that the majority of IGF-1Rs are localized at the presynaptic site and that presynaptic IGF-1Rs are normally activated under resting conditions, elevating evoked release probability (*P*r), while suppressing spontaneous vesicle release at excitatory hippocampal synapses. Acute IGF-1R blockade or transient knockdown suppresses spike-evoked synaptic transmission and presynaptic cytosolic Ca^{2+} transients, while promoting spontaneous transmission and elevating cytosolic resting Ca^{2+} level. This dual effect on transmitter release is mediated by the mitochondria which attenuate Ca^{2+} buffering in the absence of spikes and decrease ATP production during spiking activity. Furthermore, our study reveals that IGF-1R expression / activation level inversely correlates to short-term synaptic plasticity and demonstrates that diminished IGF-1R tone rescues hippocampal hyperactivity and impaired synaptic plasticity observed in young APP/PS1 model mice. We conclude that the mitochondria, activated by IGF-1R signaling, constitute a critical regulator of information processing in hippocampal neurons by maintaining evoked-to spontaneous transmission ratio, while constraining synaptic facilitation at high frequencies. Moreover, excessive IGF-1R tone may contribute to hippocampal hyperactivity associated with Alzheimer’s disease.

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Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Title: Modulation of hippocampal synaptic transmission by the tryptophan metabolites 3-hydroxy-kynurenine (3HK) and xanthurenic acid (XA)

Authors: S. A. NEALE[1], *T. E. SALT[2,1]
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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-Hydroxy-kynurenine (3HK), a molecule arising from tryptophan, is a precursor for several kynurenines, including xanthurenic acid (XA). As we have previously shown that XA can reduce hippocampal synaptic transmission (Neale *et al* 2013), we sought to determine whether 3HK could have similar actions. Furthermore we tested the effects of the KAT inhibitor AOAA in order to investigate whether effects of 3HK could be due its conversion to XA (Salt *et al* 2016).
Parasaggital *in vitro* slice preparations were made from the brains of adult male Sprague-Dawley rats. Extracellular field recordings were made from the dentate gyrus (DG) area of the hippocampus in an interface bath at ~30°C. Field excitatory postsynaptic potential (fEPSP) responses were evoked (0.1ms pulses applied every 20s) by a bipolar stimulating electrode positioned in the lower to middle portion of the molecular layer of the DG.
Addition of XA (3mM) resulted in a reversible reduction in the fEPSP slope (8.4 ± 1.4 % reduction, n=5). These results are qualitatively similar to those we have previously obtained with XA in this experimental preparation in the mouse (Neale et.al., 2013). Addition of 0.3 mM 3HK to the perfusion medium had little effect on the fEPSP slope, whereas higher concentrations caused significant reductions in fEPSP slopes at 1mM (14.1 ± 2.0 % reduction, n=7) and 3mM (41.2 ± 4.2 % reduction, n=7). Pre-application of the non-specific KAT inhibitor amino-oxyacetic acid (AOAA; 1 mM) to the slices resulted in a significantly ($P<0.001$) lesser reduction (84.9 ± 3.7 % of control, n=5) of the fEPSP slope caused by 3mM 3HK.
In summary, we have shown that 3HK, the direct metabolic precursor of XA, has similar effects to XA in reducing synaptic transmission in the hippocampus. Furthermore, the action of 3HK could be reduced by the inhibitor AOAA. These findings are consistent with the idea that changes in 3HK levels could drive XA levels and thus produce effects on neuronal circuit function, although it does not exclude the possibility that 3HK has direct effects. Thus, malfunction of the kynurenine pathway, known to occur in diseases of the brain, could cause changes in synaptic function.
Neale SA, *et al* (2013). *Neuropsychopharmacology* 38, 1060-1067.
Salt TE, *et al* (2016). *Society for Neuroscience Abstracts*, 742.16.
Schwarcz R, *et al* (2012). *Nat Rev Neurosci* 13, 465-477.

Disclosures: S.A. Neale: None. **T.E. Salt:** None.

Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Support: Ramapo College Foundation Grant

Title: CB1 receptor mediated neurotransmission in female adolesence

Authors: *C. G. REICH, A. FERRARO, P. WIG, N. AMADA, S. O'SULLIVAN, J. BOSCARINO
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Abstract: A previous study demonstrated that hippocampal CB1 receptor (CB1R) levels are lower in female adolescent animals compared to males (Reich et al., 2009). Following 21 day exposure to chronic mild stress, CB1 increased in females while decreasing in males; thus suggesting that hippocampal CB1 responds differentially to stress depending on sex. Several other lines of converging evidence clearly indicate a functional sex difference in the endocannabinoid system and behavioral reactions to exogenous cannabinoids in both human and animals (Rubino and Paralaro, 2011). However, there remains a paucity of data how these sex differences are manifested physiologically. We, therefore, begun a series of neurophysiological investigations on the endocannabinoid system in female adolescent rats. Preliminary studies show that exogenous activation of CB1 (WIN 55-212-2) enhances excitatory neurotransmission in the CA1 of female animals, while it classically decreases excitatory transmission in males. The latter is due to a CB1-mediated suppression of glutamate release. In females, we now provide evidence that CB1-modulation of excitatory neurotransmission results from enhancement of CB1-mediated suppression of GABAergic neurotransmission (inhibitory). Preliminary observations suggest that tonic CB1 activity at GABAergic synapses provides the mechanism for augmented suppression of inhibition in females.

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Poster

659. Central Modulation

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Title: Conditional deletion of gbeta5 in sensory ganglia leads to changes in nociceptive but not pruriceptive responses in mice

Authors: *M. PANDEY[1], P. ADIKARAM[1], J.-H. ZHANG[1], A. AWE[1], A. GENIS[1], C. KITTOCK[1], C.-K. CHEN[2], W. F. SIMONDS[1]
[1]Metabolic Dis. Br., NIH, NIDDK, Bethesda, MD; [2]Ophthalmology, Baylor Col. of Med., Houston, TX

Abstract: Gβ5, an atypical member of Gβ family of proteins is an obligate binding partner of R7-RGS regulator of G protein signaling proteins. The role of Gβ5 and its interacting partners has been largely elucidated in sensory phototransduction but little is known about its role in somatosensation. R7 binding protein (R7BP) is a protein partner of R7-RGS/Gβ5 protein complex which helps in anchoring the complex to the neuronal plasma membrane and augmenting its signal regulatory activity. While testing the role of Gβ5 protein complex in somatosensation we recently discovered that R7BP plays a key role in pruriception. To further understand the function of Gβ5 in somatosensation we used a transgenic mouse with a floxed *Gnb5* allele to make a conditional knock out (KO) of Gβ5, since mice with a germline KO of Gβ5 have multiple abnormalities, making it hard to study its function. Mating the floxed *Gnb5* mice with specific Cre lines with known restricted expression patterns gave us the advantage of identifying the role of Gβ5 at the cellular level. We used two different Mice Cre lines, *Advilin Cre* and *Wnt-1 Cre* with floxed *Gnb5* to create conditional KO of Gβ5 in (a) sensory neurons, and (b) sensory and CNS neurons known to lie in the somatosensory circuit, respectively. *Advilin Cre* mice mated with a reporter mice expressing lox-STOP-lox-tdTomato revealed Cre activity specifically in dorsal root ganglia but not in spinal cord or brain tissue. However, *Wnt-1 Cre* activity in reporter mice revealed a wider expression in dorsal root ganglia, dorsal horn of spinal cord and several regions in mid brain and hind brain. Immunoblotting in *Advilin Cre*- Gβ5 floxed/floxed mice revealed a specific decrease in Gβ5 levels in dorsal root ganglia but not in spinal cord and brain. *Advilin Cre*- Gβ5 floxed mice showed no significant changes in response to pruritogenic chloroquine, 48/80 and gastrin releasing polypetide (GRP) as compared to cage matched littermates. These mice showed significant behavioral changes to pain stimulation, however, when exposed to capsaicin and mustard oil in eye wipe assays and hot plate analgesia,

but not for mechanical pain. In contrast, *Wnt-1 Cre*- Gβ5 KO mice showed significant behavioral changes to chloroquine and GRP but not 48/80 when compared to controls. These mice also showed a nociceptive phenotype similar to that of *Advilin Cre*- Gβ5 KO mice. These findings suggest that Gβ5 in sensory neurons may have a significant role to play in nociceptive signaling but not pruriceptive signaling in mice. Discovery of the functional role of Gβ5 in somatosensory signaling is important to understand its physiologic function and may allow its use as a drug target for treatment in pathologic pain or itch.

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Poster

659. Central Modulation

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NIH/NINDS F32NS086361

Title: GluN2-specific NMDA receptor regulation of synaptic transmission and excitability in the thalamus

Authors: *S. A. SWANGER, S. F. TRAYNELIS
Dept. of Pharmacol., Emory Univ., Atlanta, GA

Abstract: Communication between the cortex and thalamus is necessary for integrating cognitive, emotional, sensory, and motor information, and disrupted corticothalamic connectivity is evident in neurological disorders such as epilepsy, mood and anxiety disorders, and schizophrenia. Although corticothalamic circuits are critical for numerous brain functions and behaviors, the mechanisms controlling synaptic transmission and excitability in corticothalamic circuits remain unclear. The cortex and thalamus are reciprocally connected by glutamatergic corticothalamic and thalamocortical projections, which send collaterals to gabaergic neurons in the reticular thalamus. Reticular neurons negatively regulate thalamic circuits via feed-forward and feedback inhibition of thalamocortical neurons. In this study, we examined how synaptic and tonic N-methyl-D-aspartate receptor (NMDAR) activity regulates thalamic neurons. NMDARs are non-selective cation channels activated by co-agonists glutamate and glycine, and subject to voltage-dependent block by extracellular Mg^{+2}. NMDARs are tetrameric assemblies of two GluN1 and two GluN2 subunits, and the GluN2 subtypes (GluN2A-D) have distinct functional

properties such as deactivation rate and sensitivity to Mg^{+2} block. In reticular neurons, excitatory postsynaptic currents (EPSCs) recorded from mouse brain slices can be separated into two populations based on deactivation time course and relative size of the NMDAR component; these two EPSC populations have been proposed to be mediated by corticoreticular and thalamoreticular inputs (Deleuze and Huguenard, 2016). We found that GluN2 subunit-selective modulators affected the NMDAR component of these two EPSC populations differently, suggesting that the EPSCs may be mediated by distinct NMDAR subtypes. In addition, inhibition of GluN2C/D-containing NMDARs reduced the frequency of spontaneous inhibitory postsynaptic currents recorded from thalamocortical neurons, which we interpret to reflect decreased feed-forward inhibition from reticular neurons. NMDARs have been shown to mediate a tonic depolarizing current in reticular neurons due to activation by ambient glutamate, and our data may suggest that this tonic current is mediated GluN2C/D-containing NMDARs, which have reduced Mg^{+2} block at resting membrane potential compared to GluN2A/B. This work suggests that NMDARs have diverse functional roles in regulating synaptic transmission and excitability in the reticular thalamus, and these distinct functions may be mediated by receptors containing different GluN2 subunits.

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Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Title: Syringaresinol selectively depresses excitatory synaptic transmission in hippocampal slices through the presynaptic inhibition

Authors: *Y. CHO, W. SONG, S. YOON, K.-Y. PARK, M.-H. KIM
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Abstract: Many conventional drugs acting on the nervous system are originated from botanical sources. Psychoactive substances of plants affect the nervous system by mimicking actions of endogenous neuromodulators or neurotransmitters. Here we show that syringaresinol (SYR), a plant lignan found in Castela emoryi or Prunus mume, induces short-term depression of excitatory synaptic transmission via presynaptic modulations. Bath application of SYR transiently reduces the slopes of the field excitatory postsynaptic potentials (fEPSPs) at the hippocampal Schaffer collateral (SC)-CA1 synapse in a dose-dependent manner. This SYR-induced synaptic depression was insensitive to the blockers of NMDARs, the group I mGluRs,

and mAChRs. SYR mainly reduced excitatory synaptic transmission, while inhibitory synaptic transmission remained unchanged. However, SYR had no effect on the both conductance and desensitization of AMPARs but increased paired-pulse ratios of synaptic responses at short (20 and 50 ms) inter-stimulus intervals. These presynaptic changes were associated with the reduction of the readily releasable pool size. SYR also increased K^+-conductance in neurons, whereas Ca^{2+} currents were decreased by SYR. Collectively, our study identifies SYR as a new psychoactive compound and suggests that SYR reduces excitatory neurotransmitter release.

Disclosures: **Y. Cho:** None. **W. Song:** None. **S. Yoon:** None. **K. Park:** None. **M. Kim:** None.

Poster

659. Central Modulation

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Program#/Poster#: 659.09/D54

Topic: B.07. Synaptic Transmission

Support: WCI Grant 2015-T1-001-069

Title: Unique role of J domain of synapsin III in regulation of neurotransmitter release: Control by MAP kinase phosphorylation

Authors: *S.-H. SONG[1,2], G. J. AUGUSTINE[3]
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Abstract: Among the 3 mammalian synapsin genes, synapsin III is unique in its regulation of release of dopamine (J. Neurosci. 30:9762), glutamate (J. Neurosci. 28:10835), and GABA (J. Neurosci. 36:6742). Presumably these functional attributes are conferred by the J domain, a structure found only in synapsin III. To examine the function of the J domain, we first injected a peptide from the J domain of rat synapsin III into squid giant presynaptic terminals. This peptide reversibly inhibited synaptic transmission, while a scrambled version did not; thus, the inhibitory effect is sequence-specific. Analysis of the kinetics of synaptic depression during high-frequency stimulus trains (50 Hz) revealed that J domain peptide inhibits synaptic transmission both by reducing the size of the readily-releasable pool (RRP) and by slowing mobilization of vesicles from the reserve pool (RP) to the RRP. A J domain peptide pseudophosphorylated (JD) at a MAPK phosphorylation site (S470) inhibited synaptic transmission, while a non-phosphorylatable version (JN) did not. Thus, regulation of transmitter release by J domain is under the control of the MAPK signaling pathway. Inhibition of synaptic transmission occurred more rapidly and at lower concentrations for JD compared to J peptide, suggesting that J peptide is phosphorylated before it blocks synaptic transmission. We also examined J domain function in microisland cultured mouse hippocampal neurons. Expressing recombinant J domain did not

affect the amplitude of autaptic EPSCs. During repetitive stimulation (10 Hz), wild-type J domain slowed the time constant of synaptic depression (24.3 ± 1.2 s) compared to control neurons (13.5 ± 0.4 s). However, pseudophosphorylated J domain (S470D) accelerated the rate of synaptic depression (8.5 ± 1.2 s), while a phospho-null mutant J domain (S470A) did not (23.0 ± 1.5 s). Thus, in both squid and mouse neurons, phosphorylation of J domain controls the ability of synapsin III to regulate mobilization of RP vesicles. However, J domain is not phosphorylated by MAPK under basal conditions in mouse neurons, while it is phosphorylated within minutes in squid neurons. Immunoprecipitation indicates that recombinant J domain inhibits multimerization of synapsin IIIa, suggesting a possible molecular mechanism for J domain control of RP mobilization. In summary, our results indicate that interactions mediated by the J domain of synapsin IIIa determine the dynamics of both RRP and RP vesicles, thereby regulating neurotransmitter release. Further, this regulation is controlled by MAPK phosphorylation.

Disclosures: S. Song: None. **G.J. Augustine:** None.

Poster

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Topic: B.07. Synaptic Transmission

Support: GACR 16-03913Y

Title: Glutamate release potentiation by NMDAR-inhibiting neurosteroid pregnanolone sulfate: Implications for neuroprotection

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Abstract: NMDAR activation by synaptically released glutamate is key to synaptic plasticity and can be neuroprotective. However, excessive NMDAR activation by tonically elevated extracellular glutamate mediates excitotoxicity. Recently, we have shown that endogenous neurosteroid pregnanolone sulfate (PA-S) selectively inhibits tonically over synaptically activated NMDARs, while potentiating presynaptic glutamate release. The mechanism of the PA-S-induced increase in synaptic glutamate release, and the implications of this effect for PA-S neuroprotection are unknown.
To address the mechanism of presynaptic potentiation by PA-S, we compared PA-S and a structurally similar neurosteroid pregnenolone sulfate (PE-S), which increases mEPSC frequency in primary hippocampal cultures by elevating presynaptic [Ca^{2+}]. We confirmed that pre-treatment of cells with 10μM extracellular BAPTA-AM blocked mEPSC frequency increase caused by 2μM Ca^{2+} ionophore ionomycin (+267±132% in control; +17±6% after BAPTA-AM;

p=0.06), and by 30μM PE-S (+330±193% in control; -1±13% after BAPTA-AM, p=0.04). Surprisingly, we found that presynaptic Ca^{2+} chelation with BAPTA-AM did not block the mEPSC frequency potentiation by 100μM PA-S (+164±42% in control; +122±10% after BAPTA-AM; p=0.45), suggesting that PA-S potentiates glutamate release downstream of Ca^{2+} influx.
We used oxygen-glucose deprivation (OGD) in primary hippocampal cultures to test neuroprotective properties of PA-S in two experiments. First, we tested the effect of PA-S present during acute OGD. While NMDAR inhibition by PA-S would be expected to be neuroprotective, increased synaptic glutamate release by PA-S could exacerbate toxic glutamate buildup during OGD. We found that that the balance of PA-S actions during acute OGD results in neuroprotection (36±4% neuronal death after 1h OGD; 14±3% after OGD with 50μM D-AP5, p=0.01; 21±3% after OGD with 100μM PA-S, p=0.06). Second, stimulation of excitatory synaptic activity prior to OGD, a form of ischemic preconditioning, reduces subsequent OGD damage. Given the ability of PA-S to potentiate glutamate release, we asked whether PA-S may be an effective preconditioning stimulus. Remarkably, we found that PA-S applied for 48h prior to (but not during) 1h OGD was indeed significantly neuroprotective (neuronal death was 38±2% in control; 20±6% after preconditioning with 50μM bicuculline+500μM 4-AP, p=0.04; 24±3% after preconditioning with 100μM PA-S, p=0.03). Together, our results show that PA-S, with its unique combination of synaptic effects, is exceptionally well suited to promote neuronal survival in the face of excitotoxic challenge.

Disclosures: **T. Smejkalova:** None. **Z. Naimova:** None. **L. Vyklicky:** None.

Poster

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Topic: B.07. Synaptic Transmission

Support: NIH Grant EY10291

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Title: Gβγ specificity of inhibitory adrenergic α_{2a} receptor and its modulation of synaptic transmission

Authors: ***Y. YIM**[1], K. BETKE[1], W. MCDONALD[2], R. GILSBACH[3], Y. CHEN[4], K. HYDE[1], Q. WANG[4], L. HEIN[3], H. HAMM[1]

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Abstract: Modulation of neurotransmitter exocytosis by activated Gi/o-type G-protein coupled receptors (GPCRs) is a universal regulatory mechanism used both to avoid overstimulation and to influence circuitry. One of the known modulation mechanisms is Gβγ and soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex interaction. There are 5 Gβ and 12 Gγ subunits, but specific Gβγs activated by a given GPCR *in vivo* are not known. Presynaptic α_{2a}-adrenergic receptors (α_{2a}-ARs) in both adrenergic (auto α_{2a}-ARs) and non-adrenergic neurons (hetero α_{2a}-ARs) inhibit neurotransmitter release and affect various physiological functions such as anesthetic sparing and working memory enhancement. Here, we investigate whether auto α_{2a}-ARs in sympathetic neurons use the same Gβγ subunits as hetero α_{2a}-ARs in other neuronal types to inhibit exocytosis by interacting with SNARE. Using several mice models including transgenic Flag-α_{2a}-ARs, knock-in HA-α_{2a}-ARs, co-immunoprecipitation and mass spectrometric analysis, we have determined the Gβ and Gγ subunits that interact with auto and hetero α_{2a}-ARs and SNARE complexes. So far, we find that $G\beta_2$, $G\gamma_2$, and $G\gamma_3$ preferentially interact with activated auto α_{2a}-ARs. We also see a basal Gβγ-SNARE interaction and a 2 fold enhancement of this interaction upon the auto α_{2a}-ARs activation. Further understanding Gβγ specificity and Gβγ-SNARE interaction may offer new insights into the normal functioning of the brain, as well as better understanding of disease progression.
Funding: This work was supported by the National Institutes of Health (EY10291, MH101679, DK109204, and T32 GM07628).

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Poster

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Institut du Cerveau et de la Moelle épinière (Paris)

Title: Cannabinoid receptor expressing interneurons of layer 2/3 exhibit specific morphological and functional properties in primary and secondary visual cortical areas

Authors: *M. MONTMERLE[1], A. AGUIRRE[1], O. SCHLUETER[2], J. LOURENÇO[1], A. BACCI[1]
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Abstract: During sensory processing, the correct subjective representation and interpretation of the external world is accomplished by a constant bi-directional communication between primary and secondary sensory cortices. Yet, the synaptic rules governing the processing of sensory information in these distinct cortical areas, and the specific microcircuit players involved, are still poorly characterized. After finding that the cannabinoid receptor (CB1) is more widely expressed in secondary than in primary areas, we asked whether the neurons expressing CB1 had different properties in the two areas. CB1 is mainly expressed in large inhibitory basket cells that target the soma of other neurons, thereby modulating their output. Using whole-cell patch clamping, we found that in layer 2/3 of the primary visual area of mice (V1), CB1+ interneurons exerted strong and reliable inhibition onto pyramidal cells. Interestingly, in the secondary visual area (V2) CB1+ interneurons exerted small and unreliable inhibition onto excitatory cells. Interestingly, pharmacological blocking of CB1Rs in V2 led to a potentiation of inhibition, while in V1 this effect was not observed, suggesting that CB1 interneurons in V2 are ‘doped’ by tonically or constitutively activated receptors. Differences in the kinetics of recovery from depolarization-induced suppression of inhibition (DSI) also support this hypothesis. In addition, we found a different innervation pattern of CB1+ interneurons in the two visual areas: in V2, CB1+ interneurons projected their axons both within their cortical layer and to deeper layers, while in V1 these projections were principally intralaminar. This study suggests that different visual areas exhibit differential CB1-mediated modulation of perisomatic inhibition onto layer 2/3 pyramidal neurons. Moreover, our results show differences in microcircuit connectivity patterns, suggesting area-specific differences in the integration of visual information.

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Poster

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Title: Nociceptive input imbalance mediated by ablation of C-fibers causes plastic change of GABAergic neuronal circuits in the insular cortex

Authors: *K. YAMAMOTO[1], S. MURAYAMA, 1018310[2], M. KOBAYASHI[3]
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Abstract: Sensory experience plays critical roles in the refinement of cortical connections. The cortical plastic changes have been enthusiastically studied in the visual cortex that monocular deprivation during a juvenile period yields a strong shift of ocular dominance column toward the non-deprived eye (ocular dominance plasticity). The unbalance of signal inputs causes plasticity in visual cortex. Therefore, we hypothesized that the addition of the primary afferent fibers (Aδ and C-fiber) induces plastic changes in insular cortex (IC), which receives orofatial nociceptive inputs. To test the hypothesis, we made the model whose C-fibers were ablated by capsaicin injection and examined plastic changes of inhibitory neuronal circuits in this model. At postnatal days 1-2, neonatal rats received subcutaneous injection of capsaicin (100 mg/kg) to the base of the neck. Miniature inhibitory postsynaptic currents (mIPSCs) were recorded from excitatory pyramidal neuron (Pyr) in IC layers II/III on 18 to 28 days after injection. Unitary IPSCs (uIPSCs) were recorded from the connection between inhibitory fast-spiking interneuron (FS) and Pyr. To evaluate the precise synaptic profiles including the number of release sites, release probability, and quantal size, we employed variance-mean (V-M) analysis. To estimate the quantal size of IPSCs in FS→Pyr connections, we replaced 2 mM $[Ca^{2+}]_o$ with 4 mM Sr^{2+}, which induces asynchronous release of GABA (aIPSC). Pyr of the capsaicin-treated rats (CAP) showed the smaller amplitude of mIPSCs than Sham without changing the frequency of mIPSC. The amplitude of uIPSCs obtained from CAP was also smaller than that from Sham. V-M analysis demonstrated the smaller quantal size in CAP compared to that in Sham. On the other hand, the release probability and the number of release sites were not statistically different between them.

In agreement with the results of the mIPSCs and the quantal size of V-M analysis, the amplitude of aIPSCs in CAP was smaller than that in Sham. We demonstrated that inhibitory synaptic transmission in IC was significantly reduced by ablation of C-fibers. The suppression of postsynaptic mechanisms of $GABA_A$ receptors is likely to be an underlying mechanism of the smaller amplitude of m, u, and aIPSCs.

Disclosures: K. Yamamoto: None. **S. Murayama:** None. **M. Kobayashi:** None.

Poster

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Topic: B.07. Synaptic Transmission

Support: Psi Chi Research Grant

Title: Examining the effect of systemic oxytocin on mesolimbic dopamine transmission

Authors: *M. K. ESTES, T. G. FREELS, W. T. PRATER, M. SWAMY, D. B. LESTER
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Abstract: Oxytocin is receiving much attention for its role in maternal bonding, stress, memory and learning, and social bonding. Growing research, both preclinically and clinically, indicates oxytocin may also relieve anxiety and attenuate addictive behaviors, particularly related to psychostimulant use. Mesolimbic dopamine transmission is known to be involved in both anxiety and addiction, but the interaction between oxytocin and dopamine is not clear. The present study investigated the effects of chronic oxytocin administration on dopamine release in the nucleus accumbens (NAc). Using in vivo fixed potential amperometry with carbon fiber recording electrodes, ventral tegmental area (VTA) stimulation-evoked dopamine release was recorded in the NAc of anesthetized C57BL/6J mice following either chronic oxytocin or saline administration. The chronic pretreatment paradigm, which has shown to alter related behaviors in mice (Sobota et al., 2015), included 4 ip injections of oxytocin (1mg/kg) or saline with 48 hours between injections. During dopamine recordings, mice received an ip injection of either the dopamine reuptake blocker nomifensine (10 mg/kg) or saline. Compared to saline pretreatment, chronic oxytocin pretreatment decreased baseline dopamine release by 42.9% ($p=0.001$). Baseline dopamine half-life was also decreased following chronic oxytocin pretreatment compared to saline pretreated controls (0.19 and 0.25 sec, respectively; $p=0.039$), which indicates increased dopamine transporter (DAT) efficiency in the oxytocin pretreated mice. Nomifensine had a reduced effect following chronic oxytocin in that the percent change in dopamine half-life was significantly less than that of saline pretreated mice 20 min post injection (344.1% and 586.6%, respectively; $p=0.015$). Overall, the present study provides direct evidence

that systemic oxytocin administration can alter mesolimbic dopamine transmission. Chronic oxytocin pretreatments reduced mesolimbic dopamine transmission and attenuated the effect of a psychostimulant (nomifensine) on this well-established reward pathway. An understanding of the neural effects of oxytocin are particularly important given the potential multitudes of therapeutic uses for this drug.

Disclosures: M.K. Estes: None. **T.G. Freels:** None. **W.T. Prater:** None. **M. Swamy:** None. **D.B. Lester:** None.

Poster

659. Central Modulation

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Program#/Poster#: 659.15/D60

Topic: B.07. Synaptic Transmission

Title: Gene-based synaptic inhibition using adenovirus mediated botulinum toxin A fragments

Authors: *Y. CHEN, O. P. KEIFER, JR, L. DI, N. M. BOULIS
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Abstract: Spasticity is a debilitating disorder of motor neuron hyperexcitation characterized by involuntary muscle contractions that can be extremely painful and incapacitating. It affects more than 12 million people worldwide, and is associated with a wide spectrum of diseases, including stroke, multiple sclerosis, and cerebrospinal trauma. One of the prevailing treatments for spasticity is botulinum neurotoxin (BoNT) injection, which ameliorates excessive muscle contractions by preventing presynaptic acetylcholine (Ach) release at the neuromuscular junctions (NMJ). However, the need for repeated injections and the high cost of such treatment render this option suboptimal. In this study, we present a novel application of gene-based neuromodulation for control of spasticity by delivering transgenes containing different gene fragments of BoNT serotype A (BoNT/A) to spinal cords of rats. BoNT/A consists of a light chain (LC), which contains the catalytic domain, and a heavy chain (HC), which contains the translocation domain (TD) and the receptor-binding domain (RBD). The efficacy of different combinations of gene fragments is compared in behavioral tests, histology, and Western blotting. As a translational laboratory, our ultimate goal is to develop a gene-based neuromodulatory therapy for spasticity that can be utilized for human clinical trials.

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Poster

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Topic: B.07. Synaptic Transmission

Support: HIAS15004 Hussman Foundation Pilot Grant

Title: Functional analysis of TRIM55 gene in human induced pluripotent stem cells from individuals with idiopathic autism

Authors: *J. NESTOR[1], P. D. STEIN[2], M. W. NESTOR[2]
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Abstract: Background: GWAS studies of Patients with Autism have elucidated genetic candidates that are involved in synaptic vesicle transmission and overall electrophysiological network organization. Tripartite Motif Containing 55 (TRIM55 also known as MURF2) is a *de novo* mutation with high penetrance that has been identified in a subset of our hiPSC lines from individuals with idiopathic autism via whole genome sequencing (Cukier et a., 2014).
Objective: We have designed a Lenti-GFP-TRIM55 knock-down vector to investigate a possible role for TRIM55 synaptic transmission and overall network activity in two individuals with idiopathic autism who harbor this suspected variant.
Methods: Human induced pluripotent stem cell (hiPSC) lines from two individuals with idiopathic autism and two controls were differentiated into mixed cortical cultures using dual-SMAD inhibition protocols. After terminal differentiation and aging *in vitro* for 30 or 60 days, synaptic transmission was investigated using a chemical LTP (cLTP)-inducing protocol. Cultures were assayed using high-content imaging provided by the ThermoFisher ArrayScan XTI. The intensity of phospho-CREB staining was used to analyze the robustness of cLTP across the hiPSC - derived neuronal cultures. Multi-electrode arrays (MEAs) were then used to study the overall network activity in control and autism lines within treatment and non-treatment cLTP groups. Finally, the genetically encoded calcium indicator Gcamp6 was used to assay calcium transients in the lines.
Results: We observed a significant decrease in the network spiking activity as measured by MEA as well as the number of spontaneous somatic calcium transients in one of the lines that harbor the TRIM55 mutation but not the other. Additionally, use of the scratch assay revealed a significant decrease in the migration of both lines as compared to controls.
Conclusions: This study suggests a possible role for TRIM55 interactions with other *de novo* variants in individuals with idiopathic autism, with effects on synaptic function and cell migration.

Disclosures: J. Nestor: None. **P.D. Stein:** None. **M.W. Nestor:** None.

Poster

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Topic: B.07. Synaptic Transmission

Title: Effect of histamine H_3 receptor activation on rat prefrontal cortex dopaminergic transmission and in a model of schizophrenia

Authors: *G. AQUINO-MIRANDA[1], J. ESCAMILLA-SÁNCHEZ[2], R. GONZÁLEZ-PANTOJA[2], L. E. RAMOS-LANGUREN[3], A. BUENO-NAVA[4], C. RIOS[3], J.-A. ARIAS-MONTANO[2]
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Abstract: Alterations in the function of the prefrontal cortex (PFCx) have been related to schizophrenia. The PFCx expresses high levels of histamine H_3 receptors (H_3Rs) and it is innervated by dopaminergic neurons located in the ventral tegmental area (VTA). In this work, we set out to determine the effect of H_3R activation on dopaminergic transmission in the rat PFCx by analyzing [^{3}H]-dopamine uptake by synaptosomes and depolarization-evoked release of [^{3}H]-dopamine in slices, as well as the effect of the local administration (prelimbic cortex) of H_3R ligands in a rat model of schizophrenia. The presence of H_3Rs was confirmed by the specific binding of N-α-[methyl-^{3}H]-histamine ([^{3}H]-NMHA) to CPFx synaptosomal membranes (maximum binding, B_{max}, 274 ± 26 fmol/mg protein, K_d, 2.27 nM). [^{3}H]-NMHA binding was inhibited by the H_3R agonists histamine (inhibition constant, Ki, 21.9 nM), immepip (Ki 3.2 nM) and RAMH (Ki 6.3 nM), and by the antagonists/inverse agonists clobenpropit (Ki 24.1 nM), ciproxifan (Ki 26.6 nM) and iodophenpropit (Ki 43.4 nM). The uptake of [^{3}H]-dopamine by PFCx synaptosomes was inhibited by GBR-12909 (IC_{50} 112.2 nM), desipramine (IC_{50} 3.4 nM) and fluoxetine (IC_{50} 1,737 nM), indicating that [^{3}H]-dopamine is taken up by dopaminergic and noradrenergic nerve terminals. The uptake of [^{3}H]-dopamine was not affected by the H_3R agonist RAMH (10^{-10}-10^{-6} M). Furthermore, H_3R activation with RAMH (1 µM) or immepip (1 µM) had no effect on the depolarization-evoked release of [^{3}H]-dopamine from PFCx slices, in the presence of sulpiride (1 µM) to block D_2 autoreceptors. In the rat model of schizophrenia, the administration in the prelimbic cortex of RAMH (19.8 ng/1 µl, 1 mM) increased, but not significantly, the locomotor activity induced by the systemic administration of MK-801 (0.3 mg/kg, ip), a noncompetitive antagonist at the NMDA glutamate receptors. In contrast, RAMH inhibited significantly (-46%) the spontaneous activity of control rats. Negative symptoms in the schizophrenia model were evaluated by prepulse-inhibition (PPI) of the startle response. The

local administration of RAMH (19.8 ng/1 µl) in the prelimbic cortex prevented the inhibition of PPI induced by MK-801 (0.15 mg/kg, ip), and the effect of the H_3R agonist was blocked by the previous injection of ciproxifan (30.6 ng /1 µl), supporting a H_3R-mediated action. In perfused PFCx slices, MK-801 (10 µM) significantly inhibited depolarization-evoked [^{3}H]-dopamine release (-32.8 ± 2.62% of control values), but this effect was not modified by RAMH or ciproxifan. Our results suggest that through the activation of postsynaptic H_3Rs histamine modulates dopaminergic transmission in the prefrontal cortex

Disclosures: G. Aquino-Miranda: None. **J. Escamilla-Sánchez:** None. **R. González-Pantoja:** None. **L.E. Ramos-Languren:** None. **A. Bueno-Nava:** None. **C. Rios:** None. **J. Arias-Montano:** None.

Poster

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Topic: B.07. Synaptic Transmission

Support: JERF TENKAN 17012

Title: A study on the behavioral and neuronal phenotype of syntaxin 1B gene-ablated mice: Involvment of syntaxin 1B in the fever-associated epilepsy syndromes

Authors: *T. MISHIMA[1], T. FUJIWARA[1], T. KOFUJI[2], Y. TERAO[1], K. AKAGAWA[1]
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Abstract: Two syntaxin 1 (STX1) isoforms, HPC-1/STX1A and STX1B, are coexpressed in neurons and function as neuronal target membrane (t)-SNAREs. However, little is known about their functional differences in synaptic transmission. STX1A null mutant mice develop normally and do not show abnormalities in fast synaptic transmission, but monoaminergic transmissions are impaired (Mishima *et al*. J Neurosci, 2012). We previously reported that STX1B is primarily involved in the regulation of different types of fast synaptic vesicle exocytosis, including spontaneous and evoked release of glutamatergic and GABAergic synaptic transmission (Mishima *et al.* PloS one, 2014). Recently, mutations in the STX1B gene have been shown to cause a broad spectrum of fever-associated epilepsy syndromes. In the present study, in order to examine involvement of STX1B in pathogenesis of fever-associated epilepsy syndromes, we assessed for susceptibility to seizures induced by systemic administration of PTZ or kainic acid in STX1B gene-ablated mice. We found that STX1B heterozygote mice showed increased susceptibility to the drugs. PTZ-induced seizures were blocked by anti-convulsant drug VPA and Phenytoin. We also examined the effect of acute high temperature to burst activity of cultured neuronal networks which resembling epileptiform seizures. High temperature decreased burst

frequency in wild-type neurons but not in STX1B heterozygote neurons. To clarify the influence of temperature on synaptic functions of STX1B, we examined presynaptic properties of neurotransmitter release and transporter kinetics in glutamatergic and GABAergic synapses of cultured hippocampal neurons. Implication of STX1B in fever-associated epilepsy syndromes will be discussed.

Disclosures: T. Mishima: None. **T. Fujiwara:** None. **T. Kofuji:** None. **Y. Terao:** None. **K. Akagawa:** None.

Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Title: Spinal potentiation after hindpaw ischemia mediated by group II mGluRs and nitric oxide in mice

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Abstract: Transient ischemia of the extremities produces nerve conduction block and tingling sensation, suggesting that nerve conduction block may modulate spinal neural circuits. Previously, we have reported that spinal potentiation together with reduced mechanical thresholds for hindpaw-withdrawal reflex were produced after transient ischemia applied to the hindpaw in mice. These changes were likely mediated by group II metabotropic glutamate receptors (group II mGluRs), since they were inhibited by application of an agonist for group II mGluRs. We also reported that spinal potentiation was induced bilaterally after ischemic treatment applied only to the left hindpaw, suggesting that some diffusible messengers may be involved in these changes. In the present study, we investigated a possible role of nitric oxide (NO), one of diffusible mediators that may induce neuropathic pain in a wide area of the spinal cord. We confirmed that NO donor applied to the intrathecal space alone potentiated the cortical responses. To investigate the effects of NO application at the spinal cord, we used von Frey test. Mechanical allodynia was induced after spinal application of NO donor. The potentiation observed at the spinal cord and the cortex induced by hindpaw ischemia was clearly suppressed by spinal application of L-NG-nitroarginine methyl ester (L-NAME), an inhibitor of NO

synthase (nNOS). Furthermore, no potentiation was observed in nNOS knockout mice. To visualize NO formation in the spinal cord during hindpaw ischemia, we used diaminofluorescein-FM (DAF-FM), a fluorescent NO indicator. We found that an increase of fluorescence derived from the DAF-FM and NO complex was found at the ischemic side. A similar but slightly smaller increase was also observed at the contralateral side. These results clearly indicated the roles of NO production in the spinal and cortical potentiation. We investigated the relationship between nNOS and group II mGluRs in spinal cord. In immunohistochemical staining, we found that nNOS and group II mGluRs were present in the superficial layers of the dorsal horn. Furthermore, we confirmed some cell bodies at dorsal horn had nNOS and group II mGluRs using in situ hybridization. These results suggest that the failure of group II mGluR activation, which may be produced by nerve conduction block during hindpaw ischemia, might produce NO that triggers potentiation in spinal neural circuits. These changes might be involved in the induction of neuropathic pain.

Disclosures: **T. Onishi:** None. **T. Watanabe:** None. **M. Sasaki:** None. **Y. Kamiya:** None. **T. Kohno:** None. **M. Horie:** None. **H. Takebayashi:** None. **H. Tsukano:** None. **R. Hishida:** None. **H. Baba:** None. **K. Shibuki:** None.

Poster

659. Central Modulation

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 659.20/E2

Topic: B.07. Synaptic Transmission

Support: NIH NS088503

Title: Dysbindin deficiency modifies the expression of GABA neuron and ion permeation transcripts in the developing hippocampus

Authors: H. C. RUDOLPH[1], *J. L. LARIMORE[2], S. ZLATIC[4], M. ARNOLD[3], K. S. SINGLETON[6], R. CROSS[1], M. VORDER BRUEEGE[1], A. SWEATMAN[1], C. GARZA[1], A. WHISNANT[1], V. FAUNDEZ[5]
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Abstract: Dysbindin, a subunit of the octomeric BLOC-1 complex, is necessary for proper synaptic function and GABAerigic interneuron development. In post-mortem tissue of patients with schizophrenia, there is a significant reduction of dysbindin in the hippocampus. Dysbindin null mice and mouse models of neurodevelopmental disorders are characterized with defective GABAerigic transmission, potentially due to an observable loss of parvalbumin-positive

interneurons. This could describe a common molecular pathway is several diverse neurodevelopmental disorders. For this study, we define the transcriptome of the wild type and dysbindin null mouse. We report changes in parvalbumin in agreement with previously reported data. We further examined the number of paravlbumin-positive neurons within the subregions of the hippocampus. We also demonstrate changes in chloride co-transporters NKCC1, KCC2, and NCKX2. Additionally, we observed changes in potassium channel subunits Kcne2 and Kcnj13. This study suggests that loss of dysbindin results in altered expression of molecules that regulate the excitatory/inhibitory balance in the hippocampus.

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Poster

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Topic: B.07. Synaptic Transmission

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Title: GV-58, a novel calcium channel gating modifier, reverses aging-induced weakness in transmitter release from mouse neuromuscular synapses

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Abstract: We have studied the changes in neuromuscular junction (NMJ) structure and function as these synapses mature and undergo age-related changes. Our goal was to test the hypothesis that our newly developed calcium channel agonist gating modifier (GV-58) could provide symptomatic relief for normal aging-related NMJ weakness. First, we documented changes in NMJ organization and function with aging. Neuromuscular synapses matured to their adult form and function over the first few months after birth, and then remained relatively stable at a quantal content of about 80 for about 14-16 months. The first aging-related changes appeared to be postsynaptic as receptor staining broke apart (documented by small patches of α-bungarotoxin staining) and acetylcholine sensitivity appeared to be reduced (as evidenced by reductions in miniature endplate potential amplitude). These postsynaptic changes began at about 17-18 months of age, and progressed gradually until death (between 24-32 months of age). The hypothesized reduction in postsynaptic acetylcholine receptor sensitivity was supported by what appeared to be a presynaptic homeostatic increase in transmitter release between 18-24 months of age (quantal content averaged 131.6 + 10.4 at 20 months of age). This transient increase in

quantal content reversed, and transmitter release was reduced such that by 25-30 months of age, quantal content was significantly lower than normal adult values. This age-related biphasic time-course of changes in presynaptic quantal content gradually led to NMJs with reduced immunohistochemical staining for presynaptic markers of active zone organization (bassoon and Cav2.1 calcium channels). Interestingly, after NMJs became weaker than normal adults (quantal content averaged 23.0 ± 3.6), and before they degenerated to the point that transmitter release was nearly eliminated (endplate potentials less than 2 mV), our novel calcium channel agonist gating modifier (that prolongs mean open time) could reverse synaptic weakness (increasing quantal content to an average of 45.7 ± 6.5; or a paired analysis increase of 2.35 ± 0.3 fold). These data provide evidence that GV-58 could be developed as a symptomatic treatment for neuromuscular weakness associated with aging.

Disclosures: M. Wu: None. **J. King:** None. **S.D. Meriney:** None.

Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Support: Russian Science Foundation Grant 16-15-00235

Title: Memory-enhancing and neuroprotective drug noopept modulates synaptic activity and $[Ca^{2+}]_i$ dynamics in CA1 hippocampal neurons

Authors: *V. G. SKREBITSKY, S. N. KOLBAEV, R. V. KONDRATENKO, I. S. POVAROV
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Abstract: Proline-containig dipeptide Noopept (NP) is a structural analog of piracetam, one of the first generation nootropics. Like piracetam, NP demonstrates wide spectrum of cognition improvment as well as neuroprotective properties in vivo and in vitro although at much lower doses. Its positive effect was also confirmed in patients with mild cognitive impairment of cerebrovascular and traumatic origin, in animal models of brain ischemia, Alzheimer and Parkinson diseases (Ostrovskaya et al., 2008; Jia et al., 2011). Although the effectiveness of NP was shown in a number of studies, the mechanism of its action, cellular targets as well as affected signaling pathways are still poorly understood. Our previous results demonstrated that NP significantly increased action potential (AP) frequency in stratum radiatum (SR) interneurons and the frequency of AP-dependent IPSC in pyramidal cells. In this study, we continued this line performing direct measurements of neuronal intracellular calcium in hippocampal organotypic slices from postnatal (p6) rats. We showed for the first time that NP activated neuronal calcium dynamics in regional specific manner. It selectively increased the frequency of Ca transients in

hippocampal neurons located in SR without significant changes in pyramidal layer (SP) and basal level of Ca in all investigated neurons. The amplitude and duration of transients as well as the background level of intracellular calcium was not subject to significant changes during the NP application. Taking into account layer specificity of neuronal distribution in hippocampus we conclude that NP selectively changes intracellular calcium activity in SR interneurons without significant changes in SP neurons - preferentially pyramidal neurons. The most straightforward assumption is that NP affects glutamate or cholinergic transmission. Besides the fact that both types of synapses are abundant in CA1, they also have Ca-permeable postsynaptic targets selectively expressed in SR interneuron: Ca-permeable AMPAR (Buldakova et al.,2007) and alpha 7-containing nicotinic AChR (Khiroug et al., 2003). Selective stimulation of cholinergic transmission may explain compensatory effect of NP in experimental models of memory loss (Belnik et al.,2007) and augmentation of response to exogenous ACh (Ostrovskaya et al., 2001). Involvement of cholinergic transmission is supported by our preliminary electrophysiological results demonstrating the block of NP effect on IPSCs in pyramidal neurons by methyllycaconitine -selective antagonists of alpha 7-containing nicotinic AChR. Additional experiments are required to elucidate the target of NP effect.

Disclosures: V.G. Skrebitsky: None. **S.N. Kolbaev:** None. **R.V. Kondratenko:** None. **I.S. Povarov:** None.

Poster

659. Central Modulation

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Support: DBT-Wellcome Trust India Alliance

DBT-IYBA Grant

Title: CASY-1, an ortholog of mammalian Calsyntenins regulates GABA release at *C. elegans* neuromuscular junction in an isoform-specific manner

Authors: *S. THAPLIYAL[1], Y. DONG[2,3], A. VASUDEVAN[4], J. BAI[2,3], S. P. KOUSHIKA[4], K. BABU[1]
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Abstract: Abstract:
A remarkable feature of nervous system is the specific connections between the neurons that are

responsible for the orchestrated neural networks and circuitry of our brain. Considering the complexity of the nervous system, a tightly controlled spatial and temporal regulation of several different classes of cell adhesion molecules (CAMs) is essential. Existing literature highlighting the role of neural CAMs suggests that CAMs are not only specific to adhesion but are also required for various aspects of synapse development and function.
GABA is a neurotransmitter that is functional in both vertebrate and invertebrate nervous systems. In vertebrates, 30-40% of the CNS synapses are thought to be GABAergic and alterations in GABAergic neurotransmission have been associated with several different neurological disorders. Despite, such an important role in the nervous system, our knowledge about the regulation of GABAergic neurotransmission has just started to evolve. In this study, we are proposing a novel role of CASY-1, a *C. elegans* ortholog of the mammalian Calsyntenins, in regulating GABAergic neurotransmission at the *C. elegans* NMJ in an isoform-specific manner. Despite considerable reports of involvement of Calsyntenins in GABAergic synapse development and function, it has been very difficult to deduce the cellular and molecular mechanisms and implications of these proteins on animal behavior and function.
The *C. elegans* homolog of mammalian Calsyntenins, *casy-1,* is an evolutionarily conserved type I transmembrane protein that is highly enriched in the nervous system. We report here a crucial role of *casy-1* in regulating GABAergic synaptic transmission at the *C. elegans* neuromuscular junction (NMJ) in an isoform-specific manner. The shorter isoforms of *casy-1,* CASY-1B and CASY-1C, express and function in GABAergic motor neurons to regulate GABA neurotransmission. Using pharmacological, behavioral, electrophysiological and optogenetic approaches we have established that GABA release is compromised at the NMJ in *casy-1* mutants. Further, we demonstrate that CASY-1B and CASY-1C functions in GABAergic motor neurons to modulate the release kinetics of GABA by direct interaction with the synaptic vesicle (SV) precursor motor, UNC-104/KIF1A, which is indispensable for the trafficking of synaptic proteins at the synapse. In this study, we propose a mechanism for how *casy-1*, a non-classical Cadherin can shape the functioning of the synapse and suggest a possible model for the regulation of GABAergic synaptic functioning in the mammalian brain by Calsyntenins.

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Poster

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ERDF and MEYS, CZ.1.05/1.1.00/02.0109 BIOCEV

Title: Augmentation of purinergic modulation of GABA-ergic transmission in the supraoptic nucleus during intense hormone secretion

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Abstract: The supraoptic nuclei (SON) of the hypothalamus produce hormones vasopressin and oxytocin that play important roles in the water balance, blood pressure, parturition and lactation. The release of hormones is dependent on the rate and pattern of neuronal electrical activity that is regulated by glutamatergic, excitatory, and gamma-aminobutyric acid (GABA)ergic, inhibitory, synaptic inputs. ATP has been shown previously to be the major neuromodulator of SON neurons that potentiates glutamate and GABA release by activating presynaptic and extrasynaptic P2X receptors. Although presynaptic P2X responses have been described in many parts of the brain, the precise physiological function of this form of presynaptic facilitation is unknown. Therefore, in the current study we investigated purinergic facilitation under conditions of physiologically-induced increases in the activity of magnocellular neurons. Secretion of vasopressin and oxytocin is potentiated after short term fasting and subsequent refeeding. We examined changes in the P2X receptor-mediated modulation of GABAergic transmission in the SON during food state-related changes in hormone secretion. Experiments were performed on hypothalamic slices prepared from 30-day-old rats under provision of food ad libidum and rats after 48h of fasting and subsequent refeeding with standard chow. In normally fed rats, application of ATP evoked somatic current and increased the frequency of spontaneous GABAergic postsynaptic currents (sIPSCs) in about 50 % of SON and similar effect was observed in rats refed after fasting. However, the amplitude of ATP-induced inward current was higher in refed animals (118 ± 22 pA) as compared with normally fed rats (70 ±15 pA). The averaged basal frequency of sIPSC was also similar in control and refed rats, 2.71 ± 0.23 Hz and 2.11 ± 0.22 Hz, respectively. Application of ATP induced increase in the frequency of sIPSCs in 63 % of neurons from control rats (by 1264±202%) and in 83% of neurons from refed rats (by 1833±641 %), without changing their amplitude. In neurons without somatic ATP-induced current (accumulating evidence indicate that these cells are oxytocin neurons), ATP increased the frequency of sIPSC by 207±22% and 231±96 % in control and refed rats, respectively. In conclusion, we observed a significant increase in the effect of ATP within the SON of refed vs normal rats, suggesting that rapid alteration of purinergic signaling may occur in association with potentiated hormone release.

Disclosures: **M. Ivetic:** None. **A. Bhattacharyya:** None. **H. Zemkova:** None.

Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Support: Brain & Behavior Research Foundation

Title: Divergent effects of loss of diazepam binding inhibitor signaling on synaptic inhibition in hippocampal CA1 and dentate gyrus

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Abstract: The diazepam binding inhibitor (DBI) peptide family is ubiquitously expressed in cells and highly conserved in all eukaryotic species. Though primarily studied as an intracellular signaling molecule critical in lipid metabolism, evidence is growing that DBI can be secreted extracellularly in the brain and modulate gamma-aminobutyric acid (GABA) type-A receptors ($GABA_ARs$). However, the precise roles DBI plays in GABAergic neurotransmission are largely undefined, as DBI-dependent modulation of $GABA_ARs$ appears to be specifically localized in certain areas of the brain, and DBI and/or DBI fragments may exert both agonist and inverse agonist actions. DBI may also indirectly impact $GABA_ARs$ by modulation of neurosteroidogenesis. Whether DBI signaling modulates GABAergic transmission in the hippocampus has not yet been demonstrated. To assess the impact of genetic loss of DBI on synaptic inhibition in the hippocampus, we made whole-cell voltage-clamp recordings in CA1 pyramidal cells and dentate gyrus (DG) granule cells in acute brain slices from DBI wild-type (WT) and knockout (KO) mice. Miniature inhibitory postsynaptic currents (mIPSCs) were recorded at room temperature in the presence of tetrodotoxin and ionotropic glutamate receptor antagonists kynurenic acid or APV and DNQX. In CA1, we observed an increase in mIPSC amplitude in cells from DBI KO mice (n=14 cells, 39.67 ± 1.37 pA) compared to WT mice (n=10 cells, 34.34 ± 1.68 pA) ($p=1.53^{-4}$, Kolmogorov-Smirnov [KS] test). By contrast, in DG granule cells mIPSC amplitude was reduced in cells from DBI KO mice (n=11 cells, 32.74 ± 1.29 pA) compared to WT mice (n=9 cells, 43.62 ± 2.05 pA) ($p=2.14^{-21}$, KS test). In DG, mIPSC frequency was also reduced in the KO mice (1.45 ± .08 Hz) (p=.0013, Student's t-test), but decay time was increased (35.04 ± 1.73 ms) ($p=4.03^{-8}$, KS test) compared to cells from WT mice (frequency 2.71 ± .35 Hz; decay time 29.93 ± 1.37 ms). In CA1, neither frequency nor decay time were different between WT and KO. At this time, we cannot yet rule out that at least some of these changes reflect altered neuronal and synaptic development, which may be influenced by DBI actions of $GABA_ARs$, or compensatory changes in $GABA_AR$ subunit composition. The

present results, however, indicate that genetic loss of DBI impacts synaptic inhibition in the adult hippocampus, and that the directions of DBI-mediated modulation of inhibition can vary discretely between specific subregions of the same larger brain structure.

Disclosures: C.D. Courtney: None. **C.A. Christian:** None.

Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Title: Combining pharmacogenetic neuromodulation by DREADDs with imaging brain-wide functional connectivity in wildtype mice

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Abstract: Motivation: Complex behavior is a result of numerous interactions of anatomically connected brain regions, forming specialized circuits. Current research suggests that variety of neurodevelopmental and psychiatric disorders, such as Autism Spectrum Disorder, schizophrenia and depression may be associated with altered connectivity within specific brain circuits. One popular method for estimating brain-wide functional connectivity patterns is resting-state functional magnetic resonance imaging (rs-fMRI), however, it is unclear whether this macroscopic measure is sensitive enough to capture small alterations of neural activity. To answer this question we combine rs-fMRI with circuit specific neuromodulation of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) (Urban and Roth, 2015). As a first step we asked whether modulating neural activity within the somatosensory-striatal network, a structurally and functionally well-known circuit, translates into macroscale functional connectomic changes as measured by a DREADD-fMRI approach.
Methodology: Primary somatosensory cortex of wildtype mice is targeted with DREADDs causing either neuronal inhibition or excitation (AAV-hSyn-hM4Di/hM3Dq-mCherry). Three to four weeks upon surgery, anaesthetized mice are scanned using a 7T scanner, equipped with a cryogenic coil. Rs-fMRI gradient echo EPIs are acquired for 60 minutes (3600 repetitions, TR=1s), while CNO is intravenously injected after 15 minutes from the scan start to activate the DREADDs. Rs-fMRI data are cleaned from artifacts and analyzed via seed-based approaches and dynamic connectivity analyses (Zerbi et al., 2015). CNO-induced changes in brain connectivity within the somatosensory network are compared between DREADDs- and SHAM-

operated mice. Standard immunohistochemistry protocols are used to validate the DREADDs expression.
Expected outcome and impact: First results indicate that functional connectivity of somatosensory cortex is significantly modulated by CNO such that inhibitory DREADDs cause a relative decrease and excitatory DREADDs a slight, relative increase of connectivity. Our results form the first step towards establishing a DREADD-fMRI approach to investigate the causal link between neural activity at the cell population level and markers of brain-wide, macroscopic functional connectivity as measured with rs-fMRI. Using mice as a model system is advantageous because the structural connectome is well-known and the DREADD-fMRI approach could be readily extended to disease models.

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Poster

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Topic: B.07. Synaptic Transmission

Title: xCT-mediated AMPA receptorloss in hippocampal CA3-CA1 requires mGluR5

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Abstract: Synapses in the mammalian brain are exposed to two biologically active pools of glutamate: 1) transient synaptic glutamate resulting from neuronal vesicular release and 2) ambient nonsynaptic glutamate released from both neurons and glia through a variety of molecular mechanisms. While the role of synaptic glutamate has been extensively studied, much of the function of nonsynaptic glutamate remains unknown. Several lines of evidence have shown that changes in nonsynaptic glutamate are linked to developmental, physiological, and behavioral defects in mammals. Approximately 60% of extracellular glutamate in the mouse hippocampus is released by the xCT transporter, a cystine-glutamate antiporter which is highly expressed and active on astrocytes surrounding CA1 pyramidal neurons. Mice lacking a functional xCT transporter ($xCT^{-/-}$) show both enhanced synaptic strength and increased AMPA receptor abundance at hippocampal CA3-CA1 synapses. Additionally, mutant $xCT^{-/-}$ miniature excitatory post-synaptic potentials (mEPSCs) are phenocopied by incubating control slices in glutamate-free solution. Here we show the effect of incubation in Group I metabotropic glutamate receptor (mGluR) antagonists and agonists on both control and $xCT^{-/-}$ slices and

propose a possible mechanism by which extracellular glutamate acts through mGluR5 to modulate synaptic strength at hippocampal CA3-CA1 synapses.

Disclosures: A. McRay: None. **D.E. Featherstone:** None.

Poster

659. Central Modulation

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Topic: B.07. Synaptic Transmission

Title: TrkB receptors facilitate striatonigral transmission

Authors: *P. E. REYNA, A. ÁVALOS-FUENTES, T. GARCÍA-MORENO, S. ALBARRÁN-BRAVO, F. PAZ-BERMÚDEZ, J. ACEVES-RUIZ, B. FLORÁN-GARDUÑO
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Abstract: The role of BDNF on striatonigral transmission has remained so far unknown although it is released together with dopamine from dopaminergic dendrites in substantia nigra *pars reticulata.* This study examined the pre-synaptic presence of TrkB receptors on the striato-nigral terminal and the influence of its activation on K+ depolarization-induced [3H] GABA release, as well as the signaling pathway, in nigral slices of rat. Kainic acid injected into the striatum reduced by 60% the presence of TrkB receptor protein in synaptosomes of striatonigral terminals indicating the expression of the receptors by striatonigral neurons and their transport to the terminals in *pars reticulata.* The TrkB receptor agonist, 7,8-dihydroxyflavone (7,8-DHF) dose-dependently increased the high K^+-induced GABA release. The increase was blocked by ANA-12, a selective TrkB receptor antagonist. Because D1 dopamine receptors are also present in striatonigral terminals, we examined a possible interaction between both types of receptors, since a synergistic effect on synaptic plasticity and long-term potentiation has been observed in the hippocampus. We found that the D1 receptor antagonist SCH 23390 did not completely prevent the [^{3}H] GABA release increase induced by 7,8-DHF, suggesting that both D1 and TrkB receptors act independently on [^{3}H]GABA release. Furthermore, 7,8-DHF maintained its stimulatory effect even in reserpinized rats. These results suggest an independent pathway for each receptor to bring about the increase in GABA release. U73122, a PLC inhibitor, abolished the stimulatory effect of 7,8-DHF on GABA release, suggesting that the increased release is in part, due to the increase in intracellular Ca^{2+} via IP3 receptors. Since intracellular Ca^{2+} mobilization leads to calcium-channels opening, we determined the type of channel involved. Nifedipine (10 μM) did not completely prevent GABA release facilitation by 7,8-DHF, while ω-agatoxin (1 μM) totally blocked it. These results altogether suggest that the activation of TrkB receptors present on striato-nigral terminals facilitate GABA release through a dopamine

independent mechanism that requires P/Q calcium channels. These results open a novel target for BDNF in the control of motor alterations in Parkinson's disease.

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Poster

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Topic: B.07. Synaptic Transmission

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NIHAA022292

Title: Interfering insulin/IGF-1 signaling in habenula reduces alcohol intake in rats

Authors: *W. ZUO[1], H. ZHANG[2], R. FU[3], J. YE[4]
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Abstract: Alcohol abuse is a severe socioeconomic and health problem in our society. Evidence suggests that acute and chronic ethanol exposure could induce changes in gene transcription, protein translation and post-translational modification in the nervous system. Our recent work has shown that neurons in the lateral habenula (LHb), an epithalamic structure, are very sensitive to ethanol and plays a crucial role in alcohol intake and other related behaviors. However, the underlying molecular mechanisms remain largely unknown. Chronic alcohol intake could cause major abnormalities in the central nervous system, which may be correlated with sustained impairments of insulin and insulin-like growth factor (IGF) signaling. Indeed, a recent clinical study showed a reduced reliance on glucose as the main energy substrate for resting brain metabolism in heavy drinkers (Volkow ND et al., 2015), implying that ethanol may decrease the neuronal sensitivity or response to insulin. In this study, using the phosphorylate antibodies microarray, we found that a single intraperitoneal (IP) injection of alcohol caused a robust change in insulin/IGF-1 signaling and related proteins in the habenula of rats. Conversely, acute bath application of ethanol robustly increased the frequency of spontaneous excitatory postsynaptic currents (sEPSCs), and this increase was substantially potentiated by AG1024 or picropodophyllotoxin (PPP), inhibitors of insulin and IGF-1 receptors; but was significantly attenuated by phosphatidylinositol 3-kinase (PI3-K) inhibitor, wortmannin. PI3-K is one of

major players in the insulin signaling transduction cascade. Also, a significant increase in insulin and IGF-1 receptor expression in the habenula was observed in rats treated with alcohol (2 g/kg body weight, IP) for 5, 10 or 15 days, suggesting insulin/IGF-1 resistance has occurred. Finally, intra-LHb microinjection of AG1024 (1.5 pmol, 300 nl/ side) or insulin (2 μUnit, 200 nl/side) significantly reduced alcohol intake and preference in rats in the intermittent access to 20% ethanol two-bottle free choice procedure. Together these data suggest that interfering with insulin/IGF-1 resistance by decreasing the highly-expressed receptors or elevating hormone level could reduce alcohol intake, probably a result of an increase in excitatory drive onto LHb neurons.

Disclosures: W. Zuo: None. **H. Zhang:** None. **R. Fu:** None. **J. Ye:** None.

Poster

659. Central Modulation

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: JSPS Grant-in-Aid for Scientific Research (C) (16K06989)

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Strategic Research Program for Brain Sciences in the "Development of BMI Technologies for Clinical Application"

Title: Central histamine reactivates weak memory engrams and restores apparently forgotten object memories in mice and humans

Authors: *H. NOMURA[1,2], H. MIZUTA[4], H. NORIMOTO[2], F. MASUDA[2], Y. MIURA[2], H. KOJIMA[2], A. ASHIZUKA[4], N. MATSUKAWA[4], Z. BARAKI[2], N. HITORA-IMAMURA[2], D. NAKAYAMA[2], T. ISHIKAWA[2], R. SAITO[1], Y. SANO[3], H. KUSUHARA[3], M. MINAMI[1], H. TAKAHASHI[4], Y. IKEGAYA[2]

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Abstract: Even after memories fade over long time, the lost memories may persist latently in the brain and sometimes reappear spontaneously. Reinforcement of positive modulators for retrieval of remote memory may recover the ostensibly forgotten items. However, how the retrieval of remote memory is modulated is less understood than recent memory. Thus, a method that promotes the retrieval of forgotten remote memories has not been well established. Histamine in the central nervous system is implicated in learning and memory. Histamine H_3 receptors inhibit the presynaptic release of histamine and other neurotransmitters and negatively regulate histamine synthesis. Because histamine H_3 receptors are constitutively active, their inverse agonists upregulate histamine release. Therefore, histamine H_3 receptor inverse agonists may enhance learning and memory. In this study, we examined whether histamine H_3 receptor inverse agonists enhance retrieval of remote memory and recover the forgotten remote memory in mice and humans. A single treatment of histamine H_3 receptor inverse agonists (thioperamide and betahistine) followed by memory retrieval tests restored apparently forgotten object recognition memories in mice. The treatment induced the recall of forgotten memories even 1 week and 1 month after training. Activation of histamine receptor signaling in the perirhinal cortex (PRh) was critical for thioperamide-induced memory recovery because intraperitoneal thioperamide treatment increased PRh histamine release, and intra-PRh injection of ranitidine (H_2 receptor antagonist) and ESI-09 (exchange protein directly activated by cAMP (Epac) inhibitor) blocked the thioperamide-induced memory recovery. In neuronal and neuronal circuit levels, histamine depolarized PRh neurons, enhanced their spontaneous activity, and facilitated the reactivation of behaviorally activated neurons. Chemogenetically increased spontaneous activity in the PRh was sufficient for the memory recovery. Moreover, in a human clinical trial, betahistine treatment enhanced retrieval of object recognition memory. The enhancement of memory retrieval was more evident for items that are more difficult to remember and subjects with poorer performance. These findings indicate that activation of histamine receptor signaling in the PRh boosts reactivation of weak memory engrams and restores the apparently forgotten memories.

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Poster

660. Spike Timing Dependent Plasticity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 660.01/F1

Topic: B.08. Synaptic Plasticity

Support: This work was supported in part by the Israel Science Foundation (ISF) grant number 300/16

Title: Emergence of oscillatory activity via spike timing dependent plasticity

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Abstract: Neuronal oscillatory activity has been reported in relation to a wide range of cognitive processes. In certain cases changes in the oscillatory activity have been related to pathological states. Although the specific role of these oscillations has yet to be determined, it is clear that neuronal oscillations are abundant in the central nervous system. These observations raise the question of the origin of these oscillations: are the mechanisms responsible for generation and stabilization of these oscillations genetically hard-wired or can they be acquired via a learning process? Here we focus on spike timing dependent plasticity (STDP) and ask: Can oscillatory activity emerge in a neuronal network via an unsupervised learning process of STDP dynamics? If so, how and what features of the STDP learning rule govern and stabilize the resultant oscillatory activity? To this end we studied the STDP dynamics of the effective coupling between two competing neuronal populations with reciprocal inhibitory connections. To analyze the system it is convenient to study the phase-diagram that depicts the possible dynamical states of the network as a function of the effective inhibitory couplings. This phase diagram displays a rich repertoire of possible dynamical behaviors including regions of different fixed point solutions, bi-stability and a region in which the system exhibits oscillatory activity. STDP introduces dynamics for the inhibitory couplings themselves; hence, induces a flow on the phase-diagram. We studied the STDP-induced flow on the phase diagram and investigated the conditions for the flow to converge to an oscillatory state of the neuronal network. We characterized how the features of the STDP rule govern and stabilize these oscillations.

Disclosures: M. Shamir: None. **S. Nagar:** None.

Poster

660. Spike Timing Dependent Plasticity

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 660.02/F2

Topic: B.08. Synaptic Plasticity

Support: NIH Grant DA039533

Title: Maternal deprivation modulates glutamatergic spike-timing dependent plasticity in the lateral habenula

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Abstract: The lateral habenula (LHb) is involved in reward and aversion by sending negative reward signals to monoaminergic systems. Our previous work has linked epigenetic modifications and metaplasticity of GABAergic synapses onto ventral tegmental area (VTA) dopamine neurons with a single episode of maternal deprivation (MD) as an early life stressor. Given the negative control of VTA dopamine neurons by the LHb, we extended our MD studies to the LHb and found that LHb neurons of MD rats (P21-P30) are also hyperexcitable and exhibit postsynaptic glutamatergic synaptic potentiation. Up to date no study has shown that glutamatergic synapses onto LHb neurons are capable of expressing spike-timing dependent plasticity (STDP) whose modulation could underlie MD-induced changes in LHb neuronal excitability and DA signaling from the VTA. Our study here demonstrates that glutamatergic STDP can be triggered in LHb neurons in response to near-coincident pre- and post-synaptic activities. We completely defined the STDP window using different pre post spiking order and time intervals (ranging from -50 to +50 ms). Coincident pre and postsynaptic firing is required for glutamatergic STDP of LHb neurons as pre or postsynaptic activity alone is insufficient to induce plasticity. Neither neurons displaying silent, tonic nor irregular firing pattern expressed bidirectional STDP in response to STDP induction protocols. Tonic firing neurons showed presynaptic long-term potentiation (LTP) regardless of spiking order. Instead, quiet and irregularly firing neurons expressed no plasticity or long-term depression (LTD) in response to similar protocols. This suggests that LHb neurons display activity-dependent symmetrical Hebbian STDP. LTP was abolished by bath application of an NMDA receptor antagonist (D-AP5) or inclusion of a fast calcium chelator (BAPTA) in the patch pipette, suggesting that NMDA receptors are the coincident detectors for this calcium-dependent STDP. MD impaired LTP in response to pre-post protocol (+5ms interval) and even shifted LTP toward LTD in response to post-pre protocol (-5ms interval) in tonic firing neurons suggesting an induction of metaplastcity by MD at glutamatergic synapses onto LHb neurons. The induction of STDP was

unaltered for silent and irregularly firing neurons suggesting that MD-induced metaplasticity was specific to neurons with tonic activity. We will identify the nature of the retrograde signaling molecule mediating presynaptic LTP in LHb neurons and determine whether MD-induced changes in neuromodulation of LHb neuronal activity contribute to metaplasticity of STDP.

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Poster

660. Spike Timing Dependent Plasticity

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Topic: B.08. Synaptic Plasticity

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HHMI Faculty Scholars

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Title: Disruption and repair of cortical excitatory-inhibitory balance

Authors: *R. E. FIELD[1], J. A. D'AMOUR[2], R. C. FROEMKE[3]
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Abstract: The fine tuning of inhibition to excitation is critical for spike generation, network activity, synaptic plasticity, and seizure generation (Froemke, 2015). During development, cortical excitatory-inhibitory (E:I) balance is refined in an experience-dependent manner (Dornn et al. 2010). Chronic imbalances of cortical excitation and inhibition have been found in epilepsy, autism spectrum disorders, and other neurological and psychiatric conditions (Rubenstein & Merzenich 2003; Yizhar et al. 2011). In the mature cortex, E:I balance is altered by plasticity at excitatory synapses as well as by various neuromodulatory systems (Froemke et al. 2007; Letzkus et al. 2011). As E:I balance is disrupted in some forms of epilepsy, synaptic plasticity may help repair epileptic circuits (Mathern et al. 1999). Here we examine how spike-timing-dependent plasticity (STDP) calibrates E:I balance across multiple inputs onto layer V pyramidal neurons in developing mouse auditory cortex and human temporal lobe tissue from epileptic patients. We simultaneously monitored multiple synaptic inputs onto neurons and then induced synaptic modifications by repetitively pairing single E/IPSPs with postsynaptic action potentials. Pre-before-post pairing elicited excitatory and inhibitory long-term potentiation

(LTP), while post-before-pre pairing elicited excitatory long-term depression (LTD) and inhibitory LTP (D'Amour and Froemke, 2015). In mouse auditory cortex (n=23) and human temporal lobe (n=13), manipulations at paired inputs induced heterosynaptic modifications that increased overall E:I balance. The original best excitatory input and the original best inhibitory input underwent LTD, and the overall correlation between excitation and inhibition across all channels increased (mouse auditory cortex, LTD at original best excitatory input: -22±4%, $p<0.01$, LTD at original best inhibitory input: -15±6%, $p<0.05$; human temporal lobe, LTD at original best E: -12±5%, $p<0.05$, LTD at original best I: -9±4%, $p<0.05$). In mouse auditory cortex, heterosynaptic modifications were abolished by inhibiting calcium release from internal calcium stores (n=13), providing a mechanism for regulating heterosynaptic plasticity. We are now asking if similar mechanisms are spared in the human temporal lobe. Our results show that heterosynaptic plasticity can rapidly normalize excitation and inhibition in neurotypical and epileptic circuits. Furthermore, manipulation of the excitatory-inhibitory relationship at a network level may allow for recovery of E:I balance within epileptic circuits and offer a promising approach to treating temporal lobe
epilepsy.

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Poster

660. Spike Timing Dependent Plasticity

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Program#/Poster#: 660.04/F4

Topic: B.08. Synaptic Plasticity

Title: Altered neuronal response modulation in developing cerebellar white matter following chronic perinatal hypoxia

Authors: *S. KUNDU, V. GALLO
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Abstract: White matter injury is a major feature of prematurity-related pathology in infants. Multiple lines of evidence indicate that perinatal hypoxia leads to myelination deficits and white matter (WM) abnormalities in premature neonates. At the cellular level, emerging evidence indicates that the physiology and cellular differentiation of glial precursors in the developing WM changes in response to neurotransmitter release. Previously, we have shown that in a chronic sub lethal perinatal hypoxia (Hx) mouse model GABAergic signaling between migrating interneurons and oligodendrocyte precursor cells in the cerebellar WM is significantly attenuated, leading to OPCs maturation deficits and dysmyelination. The same study also suggested that cerebellar Purkinje cells (PCs) morphologically recovered from Hx induced injury in their dendritic arborization defects at three weeks of postnatal development. Recently, we

have shown that the PCs still displayed abnormal spike activity at that age compared to their normoxic (Nx) counterpart. The impact of Hx induced injury on PCs axonal input on developing WM cells, and subsequent Hx mediated dysmyelination in WM has not been yet been determined. In the present study, we used *in vivo* extracellular multiunit recording combined with optogenetic techniques to investigate the response modulation of cells in cerebellar WM from P13 mice and define how response modulation is altered due to injury. We optogenetically stimulated PCs *in vivo*, and recorded response modulation from WM cells simultaneously. We found that responsive cells in the WM of Nx evoke 78.2% excitatory (n = 78) and 21.8% inhibitory responses upon optogenetic PCs stimulation. Strikingly, Hx completely abolished PCs evoked excitation responses in WM cells, as all 18.78% responsive cells (n=126), only displayed evoked inhibitory responses at P13. At P21, although the % of responsive cells in WM of Hx animals increased to 37.84% (n=114) all cells still evoked inhibitory response, suggesting changes in cell plasticity in WM due to Hx induced modulation of PCs axonal inputs. Finally, we also categorized responsive cells based on spike frequency and found that a larger percentage of responsive cells - perhaps OPCs displayed slow spike frequencies in Hx, as compared with responsive cells with fast spike frequencies, identified as WM interneurons. We are currently identifying these putative WM OPCs and interneurons by using different approaches. Our study uses a novel approach to shed light on neuronal modulation affecting myelination in the cerebellar WM, and how this may potentially disrupted by perinatal Hx, leading to a range of neurodevelopmental disabilities.

Disclosures: S. Kundu: None. **V. Gallo:** None.

Poster

660. Spike Timing Dependent Plasticity

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Topic: B.08. Synaptic Plasticity

Support: NIH grant R01 NS12542

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NSF ERC Center for Sensorimotor Neural Engineering (EEC-1028725)

Title: Movement-dependent electrochemical stimulation for promoting cortico-cortical plasticity

Authors: *S. MOORJANI, S. I. PERLMUTTER, E. E. FETZ
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Abstract: Hebbian conditioning paradigms seek to modulate synaptic connectivity through precisely timed activation of pre- and post-synaptic neurons. One such paradigm, developed in

our laboratory, uses action potentials recorded from one neuron to trigger delivery of electrical stimuli to neighboring cells in the motor cortex of intact monkeys.[1] Since this protocol relies on single-neuron recordings, which can be unstable over time, we are investigating movement-triggered stimulation (MTS) to induce cortico-cortical plasticity between neurons at co- and reciprocally-activated sites. Changes in cortical connectivity are directly assessed with stimulus-evoked potentials. To enhance and prolong electrical-conditioning effects, we will deliver plasticity-enhancing neuromodulators, such as brain-derived neurotrophic factor (BDNF), in conjunction with MTS.

A monkey is implanted with metal microwires and mictotubes, placed bilaterally in the sensorimotor cortex. The microtubes, interfaced with battery-operated microinfusion pumps, can administer chemicals in addition to recording neural signals and delivering electrical stimulation. The monkey is trained to perform a wrist flexion-extension target-tracking task. Movement-related activity at two cortical sites (Nrec and Nstim) is inferred from the motor output elicited by stimulation at those sites. MTS is delivered to Nstim during movements that activate neurons at Nrec. MTS is preceded and followed by delivery of test stimuli at Nrec to assess the strength of the connection to Nstim. We have found that MTS strengthens cortical connections for Nrec and Nstim sites with similar motor outputs, as seen by an increase in the size of cortical potentials evoked at Nstim, which in some cases were 150% larger after conditioning compared to preconditioning levels. Early analyses suggest that MTS increases the excitability of Nrec, creating a plastic landscape in which the monkey's wrist activity drives conditioning-induced gains even after the stimulation has ended. Importantly, the resultant plasticity persisted for up to 3 weeks after brief conditioning for 90 minutes.

We are currently characterizing the time course and activity dependence of conditioning. This will be followed by conditioning site pairs that elicit reciprocal motor outputs and, finally, delivery of BDNF at Nrec, Nstim, or both sites to test its effect on the resultant plasticity. Plastic changes arising from such electrochemical systems could provide a means to augment damaged pathways, a research direction we are currently pursuing in spinal-cord injured rats.

1. Jackson, A., Mavoori, J. & Fetz, E. E. *Nature* **444**, 56-60 (2006).

Disclosures: S. Moorjani: None. **S.I. Perlmutter:** None. **E.E. Fetz:** None.

Poster

660. Spike Timing Dependent Plasticity

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Topic: B.08. Synaptic Plasticity

Support: NSF-Grant IIS-1430296

Title: Spike-Timing dependent plasticity rules with physiological extracellular calcium concentration: Experiments and theory

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Abstract: Spike-timing dependent plasticity (STDP) is a form of synaptic plasticity controlled by the relative timing of pre- and post-synaptic activity. Positive timing between pre- and post-synaptic activity (EPSP before spike) lead to Long-Term Potentiation (LTP) whereas negative timing (spike before EPSP) induce Long-Term Depression (LTD). This plasticity involves signaling by intracellular calcium (Ca2+), suggesting that extracellular Ca2+ concentration is likely to play a critical role. Yet, most if not all in vitro STDP studies used non-physiological Ca2+ concentrations: 2-3mM, compared to the physiological range 1.3-1.8mM. Calcium-based models of STDP where Ca2+ transients result from back-propagating action potentials and EPSPs predict that the sign and magnitude of STDP depends on Ca2+ concentration. In this context, high Ca2+ concentrations could lead to an overestimate of the in vivo levels of plasticity. To investigate STDP in physiological Ca2+, CA1 pyramidal neurons in acute hippocampal slices of juvenile rats (P14-20) were recorded in whole-cell configuration. Plasticity was examined at the Schaffer collateral to CA1 synapse. With a standard pre- and post-synaptic spike pair protocol, no plasticity could be induced at 1.3mM external Ca2+, and only LTD could be induced by positive or negative time delays in 1.8mM external Ca2+. LTP is restored if the number of post-synaptic spikes was increased from 1 to 4; and with a single post-synaptic spike when the pairing frequency was increased from 0.3 to 5Hz. We built a Ca2+-based plasticity model, where LTD and LTP depend on transient changes in postsynaptic Ca2+. We found that the nonlinearity of transient calcium changes conferred by NMDA receptor activation, is critical to quantitatively account for the entire experimental dataset. In line with recent experimental work, this contribution depends on coincident firing of pre- and post-synaptic neurons, and the resulting calcium transient is endowed with a long timescale of decay. Taking into account presynaptic short term facilitation is also critical to correctly match the experimental dataset. We conclude that the STDP rule is profoundly altered in physiological Ca2+ but that a classical STDP profile can be restored under specific activity regimes.

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Poster

660. Spike Timing Dependent Plasticity

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Topic: B.08. Synaptic Plasticity

Support: UCSC Intramural funds Linea D1

R01 MH095995-A1 NIH/NIMH

Title: GSK3 modulates spike timing-dependent plasticity in layer 2/3 of somatosensory cortex through direct phosphorylation of Kv4.2 channels

Authors: G. ACETO[1], A. RE[2], A. MATTERA[1], A. S. BARBATI[1], M. RINAUDO[1], C. RIPOLI[1], F. SCALA[3], S. FUSCO[1], F. LAEZZA[4], C. GRASSI[1], *M. D'ASCENZO[1]
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Abstract: Spike timing-dependent plasticity (STDP) is an activity-dependent remodeling occurring in brain circuits. Despite its key role during development and learning the cellular and molecular mechanisms underlying STDP are still poorly understood. Here, we identified glycogen-synthase kinase 3 (GSK3) and the voltage-gated K^+ channel Kv4.2 as novel molecular targets of STDP in the mouse somatosensory cortex. We performed whole-cell patch-clamp recordings of pyramidal neurons in layer 2/3 of the mouse somatosensory cortex and studied spike timing-dependent long term depression (tLTD) in the presence of selective kinase inhibitors. We found that upon intracellular perfusion of the GSK3 inhibitor CT99021 (1 μM) the amplitude of tLTD was significantly increased compared to control conditions, while perfusion of triciribine (10 μM), an inhibitor expected to increase the level of active GSK3, resulted in an opposite phenotype. Previous studies have provided significant evidence for A-type K^+ current as a modulator of tLTD by shaping the spatio-temporal profile of dendritic back-propagating action potentials. Given that GSK3 phosphorylates Kv4.2 subunit, consequently leading to decreased A-type K^+ currents, we posited that the CT99021 would increase tLTD by inhibiting A-type K^+ current. In support of this hypothesis, bath application of 4-amynopyridine (4-AP), an A-type K^+ current inhibitor, prior to tLTD induction occluded the effect of CT99021. Furthermore, in the same neurons A-type K^+ currents were found to be bi-directionally modulated by CT99021 and triciribine. To provide a mechanistic link to these studies, HEK293 cells expressing Kv4.2 subunit were utilized for confirmatory pharmacological studies and biochemical analysis of phosphorylation of Kv4.2 at Ser-616 by GSK3. Collectively, these results identify a novel functional interaction of GSK3 with the Kv4.2 channel as a novel mechanism for STDP modulation providing novel insight into the understanding of GSK3 regulation of synaptic plasticity.

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Poster

660. Spike Timing Dependent Plasticity

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Title: The balance, the morphology, and the dendritic mosaic

Authors: *N. IANNELLA[1], T. LAUNEY[2]
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Abstract: Neurons are continuously altering the way they process information in response to changes in dynamic stimuli. Their ability for such changes ultimately relies on understanding how the interplay between synapse location, the nonlinear properties of the dendrite, and synaptic plasticity shapes the strengths and spatial arrangements of converging afferent inputs to neuronal dendrites. Both experimental and theoretical investigations support the formation of memory traces or engrams promotes the formation of clusters or hotspots of functional synapses resulting from synaptic plasticity. Our previous studies have illustrated that spike timing-dependent plasticity (STDP) can lead to synaptic efficacies arranged into spatially segregated clusters across the dendrite, which we have called a dendritic mosaic. We have recently found that the dendritic mosaic is influenced by the balance between the amount of depression and potentiation admitted by the temporal learning window describing STDP, and recently dendritic morphology also has a role to play.
Here, using a biophysically detailed neuron model of a layer 2/3 cortical cell, we find that both dendritic morphology and STDP balance has an important role to play for this spatial organization to emerge, where altering the degree of balance or the shape of the dendrite leads to changes in the occurrence and patterning of efficacy clusters. Over a broad range of STDP parameters, our model suggests that synaptic plasticity shapes the spatial arrangement of synapses in a fashion favouring the formation of efficacy clusters, however the emergence of this spatial organization is also influenced by changes in dendritic morphology. These findings suggest that under favourable conditions the branching patterns of dendrites, along synaptic plasticity leads to a subdivision of dendritic space, but such subdivision of dendritic space is

subjective in nature, appearing to be conditionally dependent function of the shape of the dendrite.

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Poster

660. Spike Timing Dependent Plasticity

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Title: GABAergic input modulates Hebbian plasticity and the free energy minimization *In vitro*

Authors: *T. ISOMURA[1,2], T. TOYOIZUMI[1], K. KOTANI[2], Y. JIMBO[2]
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Abstract: The free-energy principle predicts that neurons, synapses, and neuromodulators act to minimize unpredictability of the current sensory inputs. This free-energy principle can be implemented by the Hebbian-like synaptic plasticity rule, where changes of synaptic weights depend on the product of pre- and post-synaptic neural activities. However, the pure Hebbian plasticity is not sufficient and some extra dependency on the third factor (i.e., not pre- or postsynaptic) is required for the free energy minimization, while it is not clear if real neurons have access to this third factor.
Recent studies have reported that GABAergic input modulates synaptic plasticity of excitatory synapses. Such modulation may act as the third factor that is required for the free energy minimization. Here, we investigate whether the change in the GABAergic input affects the free energy minimization in cultured neural networks.
Rat cortical cells were dissociated and cultured on microelectrode arrays (MEAs) which have 8×8 microelectrodes embedded in the bottom of the dishes. Electrical stimulations and recordings were performed using a custom MEA system. We prepared two lines of hidden sources and induced their mixture into neural networks. The training trial was repeated 100 times. Based on recorded evoked responses, free energy was calculated in each trial.
We previously showed that response specificities of neural responses to two different source states increased. The change, which was NMDA dependent, indicates that cultured neurons learned to tune in to one source while ignoring the other (the so-called blind source separation). Moreover, free energy decreased during the training. To see the role of GABAergic input, we trained cultured neural networks in the presence of an antagonist of GABAA receptor

(bicuculline) or an agonist of benzodiazepine receptor (diazepam), and found that both bicuculline and diazepam blocked the reduction of the free energy, while retaining the Hebbian plasticity. These results suggest that GABAergic input modulates Hebbian plasticity and the free energy minimization in cultured neural networks.

Disclosures: **T. Isomura:** None. **T. Toyoizumi:** None. **K. Kotani:** None. **Y. Jimbo:** None.

Poster

660. Spike Timing Dependent Plasticity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 660.10/F10

Topic: B.08. Synaptic Plasticity

Title: Extracellular calcium influences on long-term plasticity

Authors: *R. PERIN[1], G. CHINDEMI[2], E. MÜLLER[2], H. MARKRAM[1]
[1]Brain Mind Institute, EPFL, Lausanne, Switzerland; [2]Blue Brain Project, Geneva, Switzerland

Abstract: Calcium is an essential ion involved in determining how neuronal activity impacts long-term synaptic plasticity. Here we studied the effects of varying extracellular calcium concentration on long-term potentiation in thick-tufted layer 5 pyramidal neurons of the somatosensory cortex of young rats (postnatal days 14 to 18). Patch-clamped neurons in acute brain slices *in vitro* maintained in extracellular calcium concentrations ranging from 1.2 mM to 2 mM were stimulated with long-term potentiation inducing protocols. We stimulated the presynaptic cells with trains of pulses, fitted the measured responses to the Tsodyks-Markram model of short-term plasticity and calculated the changes occurring under the different conditions to parameters such as release probability, absolute synaptic efficacy and vesicle pool recovery time constant. Our results suggest that synaptic plasticity *in vivo* should also be affected by network states which influence calcium availability at synapses.

Disclosures: **R. Perin:** None. **G. Chindemi:** None. **E. Müller:** None. **H. Markram:** None.

Poster

660. Spike Timing Dependent Plasticity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 660.11/F11

Topic: B.08. Synaptic Plasticity

Support: DFG Grant FOR2419

Title: Optogenetic induction of spike-timing-dependent plasticity at Schaffer collateral synapses in rat organotypic hippocampal slices

Authors: *M. ANISIMOVA, B. VAN BOMMEL, T. G. OERTNER, C. E. GEE
Inst. for Synaptic Physiol., Ctr. For Mol. Neurobio. Hamburg (ZMNH), Hamburg, Germany

Abstract: Modification of synaptic strength is believed to be key for the formation of memories. Whether the strength of connections is maintained as analog or digital changes remains an open question. To examine long-term changes in neuronal circuits, we are developing a method to induce synaptic plasticity without impaling or patch-clamping the pre- or postsynaptic neurons. We induce timing-dependent plasticity at Schaffer collateral synapses in rat organotypic hippocampal slices by an all-optical method, stimulating pre- and postsynaptic neurons that express channelrhodopsins that are activated by different wavelengths of light. Action potentials were evoked in CheRiff-expressing CA1 neurons with 400 nm light. ChrimsonR was expressed in CA3 cells by AAV_{Rh10} and action potentials were evoked with 635 nm light. Using this combination of opsins and wavelengths we can reliably and independently stimulate the two populations of neurons. Single action potentials were evoked in presynaptic neurons and were paired with bursts of 3 light flashes at 50 Hz to cause action potentials in the postsynaptic neurons, either after arrival of the presynaptically-evoked postsynaptic potential (EPSP, causal pairing) or prior to the EPSP (anti-causal pairing). To assess whether the strength of synaptic connections was altered by the pairing protocol, excitatory postsynaptic currents (EPSCs) were recorded from CA1 neurons while the CA3 neurons were stimulated. EPSCs from at least 2 non-transfected (i.e. non-paired) CA1 neurons were averaged and used to normalize the EPSCs recorded from transfected (i.e. paired) CA1 neurons. Three days after pairing, normalized EPSCs were significantly larger in slices that underwent causal pairing (300x at 5 Hz, ~10 ms EPSC-spike interval) than in control slices that were not stimulated with light, or slices where only the postsynaptic bursting was induced. When causal pairing was evoked at 0.1 Hz (360x), however, EPSCs of the paired neurons were not larger than in the control slices 3 days later, suggesting that all-optical STDP is frequency-dependent. Interestingly, when paired at 5 Hz, anti-causal pairing also increased EPSCs, suggesting that the LTP window is broad at this frequency. The immediate early gene c-Fos was induced in paired CA1 neurons and CA1 neurons that received only the postsynaptic stimulation. In slices where only presynaptic neurons were stimulated, c-Fos expression was not increased in CA1, confirming that CA1 neurons were not driven to burst by the CA3 input. In conclusion, our all-optical method allows us to induce plasticity at defined hippocampal synapses and to assess changes in synaptic strength days after induction.

Disclosures: M. Anisimova: None. **B. van Bommel:** None. **T.G. Oertner:** None. **C.E. Gee:** None.

Poster

660. Spike Timing Dependent Plasticity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 660.12/F12

Topic: B.08. Synaptic Plasticity

Support: ANR Dopaciumcity

INSERM

CNRS

College de France

Title: Dopamine-endocannabinoid interactions mediate spike-timing dependent potentiation in the striatum

Authors: *L. VENANCE[1], H. XU[1], S. PEREZ[1], B. DETRAUX[2], A. CORNIL[2], I. S. PROKIN[3], Y. CUI[1], B. DEGOS[1], A. DE KERCHOVE D'EXAERDE[2], H. BERRY[4]
[1]CIRB INSERM, Paris, France; [2]Univ. Libre de Bruxelles, Brussels, Belgium; [3]INRIA Rhône-Alpes, Villeurbanne, France; [4]INRIA, Villeurbanne, France

Abstract: Striatal synaptic plasticity is a key substrate for action selection and procedural learning and is tightly modulated by dopamine. Thus, characterizing the repertoire of activity-dependent plasticity in striatum and its dependence on dopamine is of crucial importance. While plasticity under prolonged activation is well elucidated, its expression in response to few spikes remains less documented. Using spike-timing dependent plasticity (STDP) as a synaptic Hebbian learning paradigm, we recently unraveled a new form of plasticity in the dorsolateral striatum: a spike-timing dependent potentiation (tLTP) induced by few coincident pre- and post-synaptic spikes (~5-15), mediated by endocannabinoids (eCB-tLTP) through a signaling pathway that relies on the activation of type-1 cannabinoid receptor (CB_1R) and transient receptor potential vanilloid type-1 (TRPV1) and on eCB dynamics (Cui et al., 2015 J Physiol; Cui et al., 2016 eLife). Thus eCBs not only promote depression but also potentiation, i.e. they act as a bidirectional system, depending on the regime of activity pattern on either side of the synapse. Whether this eCB-tLTP interacts with the dopaminergic system and consequently be affected in Parkinson's disease remains to be investigated.
Here, we report that eCB-tLTP is controlled by dopamine, impaired in Parkinson's disease and rescued by L-DOPA. We found that opto-inhibition of dopaminergic neurons prevents eCB-tLTP induction and that eCB-tLTP involves specifically dopamine type-2 receptors (D_2Rs) located presynaptically in corticostriatal glutamatergic afferents, but not D_2Rs expressed by in striatal projecting neurons (belonging to indirect pathway), cholinergic interneurons or dopaminergic

cells. Therefore, dopamine-endocannabinoid interactions via D_2Rs are required for the emergence of a tLTP in response to few coincident pre- and post-synaptic spikes and control eCB-plasticity polarity (tLTP *vs* tLTD) by modulating the eCB thresholds. We also provide a realistic mathematical model for the dynamics of the implicated signaling pathways. While usually considered as depressing synaptic function, our results show that eCBs in presence of dopamine constitute a versatile system underlying bidirectional plasticity implicated in basal ganglia pathophysiology.

Disclosures: L. Venance: None. **H. Xu:** None. **S. Perez:** None. **B. Detraux:** None. **A. Cornil:** None. **I.S. Prokin:** None. **Y. Cui:** None. **B. Degos:** None. **A. de Kerchove d'Exaerde:** None. **H. Berry:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 661.01/G1

Topic: B.08. Synaptic Plasticity

Support: Biology Aware for Research Excellence- Wright State University

Biomedical Science PhD Program

Title: Remembering how to breathe: Enhanced excitatory synaptic strength preserves motor output from the respiratory network after months of motor inactivity in bullfrogs

Authors: *J. SANTIN, M. M. VALLEJO, L. K. HARTZLER
Wright State Univ., Dayton, OH

Abstract: Compensatory plasticity of neurons stabilizes neural networks and stores memories during increases or decreases in neural activity. Most studies testing this idea use pharmacological or pathological means to alter neural activity without connecting mechanisms for network stabilization to ecologically relevant perturbations. American bullfrogs, *Lithobates catesbeianus*, undergo respiratory motor inactivity during the cold winter months (Santin & Hartzler, 2017, *J. Exp. Biol.*) because adequate skin gas exchange allows them to reside in ice-covered ponds without lung breathing at low metabolic rates. After winter, however, they produce normal respiratory motor output (Santin & Hartzler, 2016, *J. Physiol.*). We hypothesized that respiratory motoneurons undergo increases in excitatory synaptic strength and/or intrinsic excitability to preserve respiratory network output following 2-3 months of respiratory inactivity. To test this hypothesis we measured miniature excitatory postsynaptic currents (mEPSCs) and intrinsic neuronal properties using whole-cell patch clamp in labeled vagal motoneurons of the laryngeal branch from adult bullfrogs. We found that amplitude and charge transfer, but not

frequency, of mEPSCs mediated by AMPA receptors increased after winter inactivity (WI) (Amplitude: 17.4±1.3 pA *vs*.24.3±2.0, p=0.007; Charge transfer: 128.0±13.6 fC *vs.* 216.9±25.5 fC, p=0.001; Frequency: 10.1±2.2 Hz *vs.* 10.65±1.2 Hz, p=0.822). Rank ordering mEPSC amplitudes from control and WI distributions generated a scaling factor of 1.51. Dividing the cumulative distribution of mESPC amplitudes from WI motoneurons by the scaling factor produced a scaled distribution that overlaid the control distribution (Kolmogorov-Smirnov test; p=0.08). WI did not alter membrane potential, input resistance, and firing frequency-current relationship (p>0.5 for all). To determine if increases in excitatory synaptic strength on motoneurons preserve output from the respiratory network after months of inactivity, we recorded vagal nerve discharge from an *in vitro* brainstem preparation that produces respiratory burst activity resembling breathing *in vivo*. We demonstrate that a sub-saturating concentration of AMPA receptor antagonist (4 μM DNQX) does not influence the amplitude respiratory motor bursts in control bullfrogs; however, after WI DNQX reduced amplitude by 36.7±9.7% (p=0.005). This indicates that increased excitatory synaptic strength on respiratory motoneurons preserves motor output after months of natural inactivity linking mechanisms of compensatory neural plasticity to a critical adaptation for survival in an animal.

Disclosures: **J. Santin:** None. **M.M. Vallejo:** None. **L.K. Hartzler:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: B.08. Synaptic Plasticity

Support: Herchel Smith Graduate Fellowship, Harvard University

National Institutes of Health-R01DC009836

Lauer Tinnitus Research Center

Title: Visualizing homeostatic normalization in the output of long-range auditory subcortical projection neurons following a sudden drop in peripheral afferent drive

Authors: *M. ASOKAN[1,2], R. S. WILLIAMSON[2], K. E. HANCOCK[2], D. B. POLLEY[3,2]
[1]Speech and Hearing Biosci. and Technol., Harvard University, Div. of Med. Sci., Cambridge, MA; [2]Massachusetts Eye and Ear Infirmary, Boston, MA; [3]Otolaryngology, Harvard Med. Sch., Boston, MA

Abstract: Following a sudden loss of peripheral input, cortical inhibition plummets and never fully recovers. Presumably, cortical disinhibition helps to compensate for the drop in afferent drive and restores the net output from the cortical column to its homeostatic set point. To test this

directly, we tracked daily changes in layer 5 (L5) projection neurons in the auditory cortex before and after a selective loss of auditory nerve afferent synapses. The excitability of L5 subcortical projection neurons was measured directly by expressing a genetically encoded calcium indicator, GCaMP6s, and directly visualizing sound-evoked signals from L5 cortical axons on the dorsal cap of the inferior colliculus in awake, head-fixed adult mice. After several days of imaging stable sound-evoked L5 corticocollicular (CCol) activity in a baseline state, mice were exposed to moderate noise that caused only a temporary shift in cochlear and brainstem thresholds but a permanent loss of auditory nerve afferent synapses. We found that the auditory gain of CCol responses dropped the day after noise exposure but then spiked, exceeding baseline levels for several days before returning to baseline. These findings reveal short-term dynamics in the auditory corticofugal pathway following cochlear synaptopathy and suggest that local circuit changes in the auditory cortex might allow corticofugal projection neurons to stabilize their output in the face of large swings in afferent drive. Our ongoing work examines the local circuit mechanisms that support this homeostatic plasticity.

Disclosures: **M. Asokan:** None. **R.S. Williamson:** None. **K.E. Hancock:** None. **D.B. Polley:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

Location: Halls A-C

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Topic: B.08. Synaptic Plasticity

Support: NIDCD Grant F32 DC015710-01

NIDCD Grant R01 DC009836

Lauer Center for Tinnitus Research

Title: Synergistic shifts in AMPA and $GABA_A$ receptor transcripts underlying recovered auditory processing in the adult auditory cortex following peripheral denervation

Authors: *P. BALARAM[1,2], D. B. POLLEY[1,2]
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Abstract: A selective, near-complete loss of cochlear afferent nerve fibers depresses sound-evoked activity at early stages of the auditory pathway but causes a paradoxical increase in activity at the level of auditory cortex (ACtx). Increased “central gain” is associated with variable levels of recovered cortical processing; some mice regain normal auditory thresholds while other mice show no recovery of auditory processing, despite an equivalent loss of cochlear

afferent synapses and auditory brainstem responses.
How do auditory cortical neurons recover responses to sound following peripheral denervation? We hypothesized that homeostatic regulation of AMPA and $GABA_A$ postsynaptic receptors would contribute to central gain after neuropathy, and might explain functional outcomes for sensory processing between individuals. Further, homeostatic regulation of postsynaptic receptors could differ between excitatory and inhibitory cortical neurons, and the opposing directions of receptor shifts between these two populations could work synergistically to maximally increase central gain.
To address these questions, we measured sound-evoked responses in awake, adult head-fixed mice using widefield and two-photon imaging of cortical neurons expressing GCaMP6s under control of the CAMKIIa promoter. We tracked daily changes in sound-evoked responses for five days following near-complete denervation of cochlear afferent nerve fibers and documented variable levels of damage and functional recovery between mice. We quantified transcriptional levels in genes that encode AMPA and $GABA_A$ receptor subunits in individual auditory cortical neurons. Changes in the transcription of these subunits reflect subsequent changes in the translation of AMPA and $GABA_A$ receptors, thus providing a correlative measure of synaptic scaling in ACtx.
Cortical neurons were chemotyped by documenting the expression of *VGLUT1* or *VGLUT2* mRNA (excitatory neurons), or *VGAT* mRNA (inhibitory neurons). Expression levels of *Gria2* mRNA, which encodes the GluA2 subunit of AMPA receptors, and *Gabra1* mRNA, which encodes the α1 subunit of $GABA_A$ receptors, were separately quantified in *VGLUT*-positive and *VGAT*-positive neurons across ACtx layers (L)2/3, L4 and L5/6 . Following neuropathy, *Gria2* and *Gabra1* transcripts were significantly shifted relative to sham-operated controls, with complementary transcriptional shifts between *VGLUT*-positive and *VGAT*-positive neurons. These synergistic transcriptional shifts across local cortical networks may provide the means to increase the gain on reduced afferent inputs and recover normal activity levels in the ACtx.

Disclosures: P. Balaram: None. **D.B. Polley:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 661.04/G4

Topic: B.08. Synaptic Plasticity

Support: NIH R21 MH105706

Title: Neurotransmitter switching in the adult mouse hippocampus and changes in episodic memory

Authors: *S. ZAMBETTI, J. O. CONNORS, N. C. SPITZER
Biol. Sci., UC San Diego, LA Jolla, CA

Abstract: Neurotransmitter (NT) switching is a newly recognized form of plasticity in which neurons acquire a novel function by changing the NT that is expressed and released, allowing the brain to adapt to internal and external stimuli. Extensively investigated in the developing Xenopus nervous system (Spitzer, 2017), it has recently been discovered in adult rodents (Dulcis et al., 2013).
We previously showed that one week of running induces disappearance of a thousand neuropeptide Y (NPY)- expressing neurons and appearance of an additional thousand VGluT1-expressing neurons in the hilus of the dentate gyrus (DG) of adult mice. The loss of NPY neurons was associated with a decrease in the NPY fiber density in the molecular layer (ML) of the DG, to which the NPY neurons project (Deller & Leranth 1990). No cell death or neurogenesis was associated with these changes in the hilus although increased neurogenesis was observed in the subgranular zone.
We now report that animals that have been running for four weeks still exhibit the changes in the number of NPY and glutamatergic neurons observed after just one week of running. However, mice that have been running for one week and then deprived of the running wheel for another week present no change in number of NPY and glutamatergic neurons compared to controls, demonstrating the reversibility of the change.
In addition, we have investigated the involvement of NPY-Glu switching in the behavioral outcome of running. Three weeks of running increase episodic memory evaluated with the object recognition test (Bolz et al., 2015). We found that mice spend more time interacting with the novel object than the familiar one after one week of running, compared to controls. Furthermore, animals that have been resting for one or two weeks after running for one week still performed better than controls, suggesting that NPY-Glu switching may contribute to a long lasting effect on the DG circuit. We hypothesize that the loss of NPY neurons affects the response of mature and new born granule cells (GC) to entorhinal cortical (EC) input. NPY fibers are enriched in the projection zone of the lateral EC (Amaral et al., 2007) and NPY can regulate the release of Glu (Silva et al., 2003). Thus, the decrease in NPY neurons may trigger a long lasting potentiation of the EC-GC connections.
To dissect the involvement of NT switching in the regulation of neurogenesis and the increase memory performance we will prevent the loss of NPY and the gain of Glu expression using Cre-dependent viruses expressing NPY and a small interference (si) VGlut1 stereotaxically injected into the DG of NPY-Cre mice (Shi et al., 2013) before the onset of the running period.
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Disclosures: S. Zambetti: None. **J.O. Connors:** None. **N.C. Spitzer:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

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Topic: B.08. Synaptic Plasticity

Support: Ellison Medical Foundation

W.M. Keck Foundation

Title: Regulation of motor coordination by neurotransmitter switching in the brainstem

Authors: *H. LI, N. C. SPITZER
Neurobio. Section, Div. of Biol. Sciences, Kavli Inst. for Brain, UC San Diego, La Jolla, CA

Abstract: Motor control is required for accurate movement and can be disrupted in natural aging or motor disorders, e.g. ataxia. Exercise is a therapy that improves motor coordination but the mechanism is obscure. Neurotransmitter (NT) switching is a newly appreciated form of plasticity in the adult brain (Spitzer, 2017). Here we report exercise-induced NT switching in motor circuits and its role in motor control.

Adult mice given free access to running wheels for 1 week had enhanced motor coordination compared to non-runner controls, exemplified by a higher speed at fall from an accelerating rotarod and a shorter time to cross a balance beam. We then examined whether running induced NT switching in motor circuits and discovered the disappearance of ~600 ChAT (choline acetyltransferase) neurons and the appearance of an additional ~600 GAD1 (glutamate decarboxylase 1) neurons in the caudal pedunculopontine nucleus (cPPN) of runners compared to controls. No neuronal death or neurogenesis was detected.

The loss of ChAT and gain of GAD1 both occur in the same neuronal population. Neuronal nitric oxide synthase (nNOS), which is co-localized with ChAT in the cPPN and did not change with running, was used as a cell marker to label ChAT neurons. Triple-staining ChAT mRNA, GAD1 mRNA and nNOS protein revealed a decrease in ChAT and an increase in GAD1 transcripts in nNOS cells in runners compared with controls.

To test for causality between NT switching and behavioral change, we overexpressed ChAT in the cPPN by injection of ChAT-Cre mice with AAV-DIO-ChAT-mRuby2 and found it prevented the improvement in motor coordination gained by running. Expression of a control virus (AAV-DIO-mRuby2) did not affect the improvement. These findings suggest that NT switching is necessary for the enhancement of motor coordination. We are now testing the behavioral consequence of suppressing the increase in expression of GAD1 with AAV-DIO-GAD1shRNA.

To learn how NT switching regulates coordination, we will co-label retrograde tracers, ChAT mRNA, and nNOS protein to determine the target nuclei of the neurons that switch their NT.

The reversibility of behavioral changes and NT switching was tested when running wheels were

removed after 1 week of running. Strikingly, runners sustained better performance than controls in the re-test after 1 week of rest although the numbers of ChAT and GAD1 neurons were not different from controls. The results suggest that NT switching was reversed but improvement in learned skills was sustained for at least 1 week. We are currently investigating how long the enhancement of coordination is sustained.

Disclosures: H. Li: None. **N.C. Spitzer:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 661.06/G6

Topic: B.08. Synaptic Plasticity

Support: WM Keck Foundation

Title: Environmental models of Autism engage neurotransmitter switching in prefrontal cortex

Authors: *S. K. GODAVARTHI, N. C. SPITZER
Neurosci., Univ. of California San Diego, San Diego, CA

Abstract: Neurotransmitter switching (NTS) is a form of homeostatic plasticity characterized by loss of one NT and gain of another in the same neuron (Spitzer, 2017). NTS is essential for normal CNS development (Misgeld et al., 2002; Root et al., 2008) and generally involves a change in the sign of the synapse from excitatory to inhibitory or vice versa. This raises the possibility that NTS could contribute to neurodevelopmental disorders, often characterized by excitation-inhibition imbalances. We are investigating the role of inadvertent and unwanted NTS in emergence of autism spectrum disorders (ASDs), focusing on prefrontal cortex (PFC), a key region implicated in ASDs.

Using environmental models of autism (EMA), developed by injecting valproate or poly Inosine:Cytosine in pregnant dams at E12.5, we previously reported loss of ~6000 GAD67+ neurons and gain of ~6000 vGluT1+ neurons in the medial PFC (mPFC) in postnatal day 10 (P10) EMA mice with respect to control mice. Absence of changes in cell death and total neuronal number indicate that there is respecification of GAD67+ in mPFC of EMA mice with vGluT1 as the switching partner. Parvalbumin (PV)+ (~4000) and Cholecystokinin (CCK)+ (~2000) inhibitory neurons account for the GAD67+ reduction.

In order to assess how early the switch occurs and how long it persists, we examined EMA mice for NT changes in an age-dependent manner. At embryonic day 18.5 (E18.5), there is no difference in the number of Dlx2+ neurons and Tbr1+ neurons (inhibitory and excitatory progenitor neuron markers respectively) between EMA and control animals, suggesting that the switch is a postnatal phenomenon. Similar to P10, there is a reduction of ~7000 GAD67+

neurons, and gain of ~7000 vGluT1+ neurons at P25. At P30, although the difference is smaller, there is still a loss of ~2000 GAD67+ neurons and gain of ~2000 vGluT1+ neurons. mPFC cells positive for both GAD67 and vGluT1 further support the switching partnership.
By P90 there is no difference in the GAD67+ and vGluT1+ neuron numbers between control and EMA mice. Thus, the switch does not persist into adulthood. As expected, P90 EMA mice show symptoms associated with autistic behavior- stereotypical and repetitive behavior and reduced social-interaction.
Early-postnatal NTS in EMA mice may affect the trajectory of PFC development, although NT balance is recovered in adulthood. The altered circuits in turn may lead to altered behavior. We will test this hypothesis by preventing NTS by overexpressing GAD67 and knocking down vGluT1 specifically in PV neurons of early-postnatal PV-Cre mice, to learn if it rescues the behavioral deficits.

Disclosures: S.K. Godavarthi: None. **N.C. Spitzer:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

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HFSP Long-Term Fellowship

Title: Plasticity of identified, functionally heterogeneous synapses shapes cell-wide plasticity of V1 neurons *In vivo*

Authors: *S. EL BOUSTANI[1,2], J. IP[2], V. BRETON-PROVENCHER[2], H. OKUNO[3], H. BITO[4], M. SUR[2]
[1]EPFL, Lausanne, Switzerland; [2]Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA; [3]SK project, Med. Innov Ctr., Kyoto Univ. Grad Schl of Med., Kyoto, Japan; [4]Univ. Tokyo Grad Sch. Med., Tokyo, Japan

Abstract: Neuronal circuits in the developing and mature brain are subject to dramatic changes driven by sensory inputs or motor learning, causing individual cells to modify their responses to individual inputs while maintaining a relatively stable level of overall activity. Cell-wide homeostatic plasticity was initially reported as a global mechanism for stabilizing the output

firing rate of a cell by uniformly scaling up or down the effective strength of all its synapses. More recent experimental evidence in vitro has suggested the existence of local homeostatic mechanisms acting at the level of dendritic stretches or even at single synapses that would potentially confer rich functional compartmentalization within the dendritic tree. However, the existence and nature of local homeostatic plasticity in vivo and its implications for the coherent reorganization of single cell responses remains unexplored. Here we have used visual-optogenetic pairing to demonstrate that induction of receptive field plasticity in single visual cortex neurons of awake mice alters identified synapses on neuronal dendrites. Such plasticity potentiates specific synapses and depresses others within short stretches of the same dendrite, consistent with functionally heterogeneous local sets of synapses that convey diverse receptive field inputs to a neuron. Crucially, depressed spines lie in close proximity to potentiated spines, indicating coordinated Hebbian and homeostatic plasticity in vivo that involves neighboring synapses. AMPA receptors are trafficked into potentiated spines and removed from depressed spines via targeted expression of the immediate early gene product Arc in the latter spines. The spatially local distribution of depressed spines around potentiated spines, in conjunction with functionally intermixed synaptic inputs to dendrites, highlight a possible mechanism that organizes cell-wide plasticity with local dendritic interactions.

Disclosures: S. El Boustani: None. **J. Ip:** None. **V. Breton-Provencher:** None. **H. Okuno:** None. **H. Bito:** None. **M. Sur:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

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Topic: B.08. Synaptic Plasticity

Support: NIH grants EY007023

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HFSP Long-Term Fellowship

Title: Redistribution of synaptic proteins between identified synapses of V1 neurons during experience-dependent plasticity *In vivo*

Authors: *P. IP[1], S. EL-BOUSTANI[1], V. BRETON-PROVENCHER[1], H. OKUNO[2], H. BITO[3], M. SUR[1]
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Abstract: Cortical circuits are remodeled in response to changes driven by sensory inputs. Regulation of AMPA receptor (AMPAR) membrane expression and targeting of immediate early genes such as Arc is critical for synaptic plasticity. However, our understanding of the mechanisms of AMPAR and Arc targeting *in vivo* is limited, in part by a lack of time-lapse imaging strategies at the synaptic level. Furthermore, because conventional transfection methods such as viral vectors require weeks to express, they are less suitable for the expression of molecular probes to study synaptic dynamics during development. To overcome these issues, we delivered plasmids into individual neurons of mouse primary visual cortex (V1) by two-photon guided electroporation. Expression of fluorescently tagged probes in spines and dendrites enabled us to visualize surface AMPAR subunits and Arc in awake mice and to study their synaptic targeting in single, identified layer II-III neurons. We observed prominent redistribution of AMPAR and Arc in spines and along dendritic branches under different conditions *in vivo*. Ocular dominance (OD) plasticity in V1 during a critical period is a well-established model for studying experience-dependent cortical changes. V1 neurons show reduced responses from a deprived eye following monocular deprivation (MD), followed by recovery of responses when the deprived eye is re-opened. We imaged V1 neurons following MD, before and a few hours after eye re-opening during the critical period for OD plasticity, to assess how an increase in synaptic drive from the re-opened eye remodeled spines. By measuring eye-specific drive in neurons and spines in which we expressed GCaMP6s, we found that spines with input from the re-opened eye rapidly enlarged and showed reduced Arc expression, whereas nearby spines were reduced in size and showed increased Arc expression. These studies suggest that active redistribution of synaptic proteins underlies functional experience-dependent plasticity of V1 neurons.

Disclosures: P. Ip: None. **S. El-Boustani:** None. **V. Breton-Provencher:** None. **H. Okuno:** None. **H. Bito:** None. **M. Sur:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 661.09/G9

Topic: B.08. Synaptic Plasticity

Support: MRC MRes/PhD programme

Title: The role of external tufted cells in activity-dependent plasticity of the olfactory bulb

Authors: *C. HAHN, M. S. GRUBB
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Abstract: Neuronal plasticity allows networks to learn and adapt to the environment and change behaviour accordingly. The highly plastic olfactory bulb network serves as a good model to study plasticity. Olfactory bulb plasticity is viewed as primarily an interneuron phenomenon as these cells replenish throughout life and undergo activity-dependent plasticity. External tufted cells (ETC) are excitatory interneurons found in the glomerular layer of the olfactory bulb that are major modulators of olfactory sensory processing. However, surprisingly little is known about activity-dependent alterations in these neurons, though their location and monosynaptic connection to olfactory sensory neurons (OSNs) would suggest a role in adapting the network to environmental changes.
To understand whether these cells are important for adapting the olfactory network, ETC functional and structural characteristics were compared in control and 24 hour naris occluded mice. Whole-cell patch clamp recordings in acute olfactory bulb slices reveal that intrinsic excitability, assessed by multiple spiking properties, does not change with this manipulation. Additionally, ETC-characteristic spontaneous burst firing does not change in terms of number of spikes fired, or burst properties. Furthermore, neither single spike properties nor sag potential amplitude show significant differences after occlusion. However, when assessing synaptic properties, ETCs in occluded conditions have larger long lasting excitatory currents, with no change in the frequency of their occurrence. We further investigated whether occlusion results in a change in the release probability at OSN synapses by recording from ETCs while stimulating OSN axons. We found that after occlusion the paired-pulse ratio (PPR) of these inputs decreases, suggestive of an increase in release probability at OSN synapses.
These alterations are indicative of adaptive plasticity in excitatory signalling in the olfactory bulb glomerular network. They may act to control the gain of information flow through the circuit, maintaining sensory performance in the face of external perturbations.

Disclosures: C. Hahn: None. **M.S. Grubb:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: B.08. Synaptic Plasticity

Support: MRC PhD studentship

Title: Characterising dopaminergic plasticity in the mouse olfactory bulb

Authors: *D. J. BYRNE, M. S. GRUBB
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Abstract: Olfactory bulb dopaminergic neurons are inhibitory interneurons involved in the early processing of odour information in the glomerular layer. These neurons can be readily identified by the expression of tyrosine hydroxylase (TH) and comprise of two main distinct populations that can be classified based on soma size. We use a Cre-driver mouse line under the control of the dopamine transporter (DAT) to label dopaminergic neurons. Initial experiments have been to characterise this population using immunohistochemistry and induce activity-dependent changes by unilateral naris occlusion. Co-localisation of DAT-tdTomato expression with TH in the mouse glomerular layer is restricted to dopaminergic neurons with a small soma size. A proportion of DAT-tdTomato neurons were found to not express TH. Co-staining with another dopaminergic marker dopa decarboxylase (DDC) reveals co-localisation with TH-positive neurons and absence from DAT-tdTomato neurons that are TH-negative. Investigating markers of other known glomerular layer neurons demonstrated that this subpopulation is part of the calretinin population of neurons. Olfactory dopaminergic neurons are known to be particularly plastic, altering their structure, function and gene expression in an activity-dependent manner. We use slice electrophysiology and immunohistochemistry to examine experience-dependent changes in DAT-tdTomato neurons after one and three days of unilateral naris occlusion. Using manual sorting, we can isolate DAT-tdTomato neurons from manipulated mice and perform targeted gene expression analysis. We have a mouse model that predominately labels a distinct subpopulation of olfactory bulb dopaminergic neurons. We can readily manipulate the activity of these neurons and to investigate how functional plasticity is regulated by activity-dependent changes in gene expression and epigenetic modifications.

Disclosures: D.J. Byrne: None. **M.S. Grubb:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

Location: Halls A-C

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Program#/Poster#: 661.11/H1

Topic: B.08. Synaptic Plasticity

Support: NIH R01-EY014882

Title: Input specific plasticity with visual experience by Homer1a mediated Metabotropic glutamate receptor 5 signaling in mouse primary visual cortex

Authors: *V. B. CHOKSHI[1], M. GAO[2], P. F. WORLEY[3], H.-K. LEE[4]
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Abstract: Sensory systems inform us about the surrounding environment. It is well accepted that sensory experience during development shapes proper functional connectivity of cortical neurons. Brain deprived of sensory inputs in early development is not able to recover its normal functionality when sensory input is restored at a later age. Hence it is important to understand the mechanisms by which cortical synapses recover function with sensory experience during an early critical period . It has been shown that depriving vision of mice (P21-P120) for two days strengthens excitatory synapses on principal neurons in layer 2/3 of primary visual cortex (V1) in an input specific manner (Petrus et al. 2015). Intracortical inputs measured as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) mediated synaptic currents are strengthened, while the strength of feed-forward excitatory inputs from layer 4 is unchanged. We found that the strength of intracortical synapses is reversed rapidly upon restoring visual experience for two hours, which requires an activity-dependent immediate early gene Homer1a (H1a). Using knockin mice that specifically lack H1a signaling through metabotropic glumatate receptor 5 (mGluR5FR KI), here we demonstrate that mGluR5-H1a signaling is critical for rapid experience-dependent homeostatic depression of intracortical synapses. Furthermore, mGluR5FR KI mice show defective ocular dominance plasticity (ODP) measured using intrinsic optical signal imaging method. Our reults suggest a key role of mGluR5 mediated H1a signaling in experience-dependent plasticity in mouse V1.

Disclosures: **V.B. Chokshi:** None. **M. Gao:** None. **P.F. Worley:** None. **H. Lee:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

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Topic: B.08. Synaptic Plasticity

Support: NIH R01-EY014882 to H.-K.L.

Title: Homeostatic plasticity of excitatory synapses in *Ex vivo* cortical circuits

Authors: *B. D. GRIER[1,2], V. CHOKSHI[3,2], A. DYKMAN[4], E. NIEBUR[1,2], H.-K. LEE[1,2]
[1]Neurosci., [2]Mind Brain Inst., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Biol., [4]Robotics, Johns Hopkins Univ., Baltimore, MD

Abstract: Synapses within the central nervous system show a remarkable ability to undergo functional change in order to store information, as in the hippocampus, or in response to changes in sensory input, as in sensory cortex. Hebbian plasticity, such as long-term potentiation and long-term depression, underlies much of the functional plasticity seen at excitatory synapses. This form of plasticity is inherently unstable however, and left unchecked, would lead to runaway potentiation and depression, resulting in neuronal firing outside of a physiologically

relevant range. Homeostatic plasticity works to preserve efficient information transfer at central nervous system synapses in the face of changing information processing needs of a system. Prolonged changes in visual experience trigger homeostatic plasticity of excitatory synapses, which has been measured *ex vivo* in primary visual cortex (V1) layer 2/3 (L2/3) pyramidal neurons (Goel et al., 2006; Goel & Lee, 2007). However, the relevant pattern of neural activity that drives such plasticity *in vivo* is currently unknown. To determine this, we aimed to develop an *ex vivo* stimulation paradigm, using acute cortical slices, that may allow parametric analysis of different components of *in vivo* activity patterns that drive homeostatic synaptic plasticity. An advantage of using this system compared to conventional neuronal cultures is that it mostly preserves *in vivo* circuitry. Recent studies using cortical slices demonstrated that homeostatic synaptic changes can be restricted to a certain set of inputs onto cortical neurons (Petrus et al., 2015), which highlights the critical need to study homeostatic synaptic plasticity in the context of a neural circuit. By stimulating V1 layer 4 to fire with biologically relevant patterns of activity, we have observed homeostatic synaptic plasticity in L2/3 pyramidal neurons. Further, by employing computational algorithms we have begun to dissect the components of neuronal firing patterns that are necessary for driving homeostatic change. Development of an *ex vivo* preparation will allow parametric analysis of the neural activity necessary for homeostatic plasticity *in vivo*, as well as provide an efficient platform to test molecular mechanisms of *in vivo* homeostatic synaptic plasticity in a reduced preparation.

Disclosures: **B.D. Grier:** None. **V. Chokshi:** None. **A. Dykman:** None. **E. Niebur:** None. **H. Lee:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

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Topic: B.08. Synaptic Plasticity

Support: PAPIIT Grant IN215816

CONACYT Grant 417634

Title: Extinction of aversive taste memory homeostatically prevents the maintenance of *In vivo* insular cortex LTP: Calcineurin requirement

Authors: *A. RIVERA-OLVERA[1], ***A. RIVERA-OLVERA**[2], J. NELSON-MORA[3], M. GONSEBATT[3], M. ESCOBAR[1]
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Abstract: Accumulating evidence indicates that homeostatic plasticity mechanisms dynamically adjust synaptic strengths to promote stability that is crucial for memory storage. Our previous studies have shown that prior training in conditioned taste aversion (CTA) prevents the subsequent induction of long-term potentiation (LTP) in the projection from the basolateral nucleus of the amygdala (BLA) to the insular cortex (IC) in vivo. We have also reported that induction of LTP in the BLA-IC pathway modifies the CTA extinction. Memory extinction involves the formation of a new associative memory that inhibits a previously conditioned association. A body of evidence suggests that protein phosphatase calcineurin (CaN) is involved in the extinction of some behavioral tasks. The aim of the present study was to analyze the effect of CTA extinction on the ability to induce subsequent LTP in the BLA-IC projection in vivo, as well as, the role of CaN in this process. Thus, 48h after CTA extinction animals received high frequency stimulation in order to induce IC-LTP. Our results show that extinction training allows the induction but not the maintenance of IC-LTP and increases the CaN expression. These findings reveal that CTA extinction promotes a homeostatic regulation of subsequent IC synaptic plasticity maintenance through increases in CaN levels. Supported by: PAPIIT IN215816 and CONACYT 417634.

Disclosures: **A. Rivera-olvera:** None. **J. Nelson-mora:** None. **M. Gonsebatt:** None. **M. Escobar:** None.

Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

Location: Halls A-C

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Title: Linking homeostasis of neurons and networks in freely behaving rats

Authors: Z. MA[1], R. WESSEL[1], G. TURRIGIANO[2], *K. B. HENGEN[3]
[1]Physics, Washington Univ. in St. Louis, Saint Louis, MO; [2]Dept of Biol., Brandeis Univ., Waltham, MA; [3]Biol., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: The rapid modifiability of neural networks, such as those in the cerebral cortex, underlies learning and cognition. However, such modifiability makes neuronal networks prone to severe destabilizing forces. Homeostatic plasticity is assumed to compensate for these effects and thus underlie the capacity of networks to be simultaneously stable and rapidly modifiable. While cell-autonomous homeostatic mechanisms have been well described in vitro and ex vivo, the assumed connection to network activity, the basis of brain function, has never been evaluated. Does the stabilization of neuronal firing rates underlie stable network dynamics?
To address this question, we investigated the dynamics of regular spiking (RS) and fast spiking (FS) neurons in the context of cortical circuit dynamics in freely behaving rats during a direct homeostatic challenge. Specifically, we obtained continuous, 16-channel extracellular (wire electrode) array recordings from visual cortex of freely behaving rats for 9 days and concurrently monitored behavioral conditions. The experimental protocol consisted of (i) three days of baseline activity and (ii) six days of monocular deprivation. We extracted single-unit spiking from the extracellular recordings using spike-sorting algorithms and distinguished between regular spiking (RS) and fast spiking (FS) units.
Based on the RS spike trains, we evaluated cortical circuit dynamics with respect to “criticality” using the measure of neuronal avalanches, which are cascades of contiguous spikes. This network analysis revealed three important features. First, during baseline cortical activity, neuronal avalanches had power law size and duration distributions. Furthermore, avalanche sizes and durations followed a scaling relation, thus providing an important evidence of a dynamical critical system. Second, following monocular deprivation, network dynamics shifted away from criticality and then recovered towards criticality within several days. Third, change of RS network dynamics (and FS firing rate) preceded RS firing rate changes.
In conclusion, these results link homeostasis of neurons and networks in freely behaving rats and raise the question to what extent FS firing rate homeostasis determines network dynamics and RS firing rate homeostasis.

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Poster

661. Homeostatic Synaptic Plasticity: *In Vivo* Activity Manipulation

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Topic: B.08. Synaptic Plasticity

Support: NIH NIDA DA029565

DA028020

DA023206

DA024570

DA031551

Title: Cascades of homeostatic dysregulation progressively intensify cocaine seeking

Authors: *J. WANG[1], M. ISHIKAWA[3], M. OTAKA[1], J. Y. KIM[1], G. R. GARDNER[1], Y. H. HUANG[2], J. W. HELL[4], R. C. MALENKA[5], M. E. WOLF[6], O. SCHLÜTER1[1], Y. DONG[1]
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Abstract: Functional output of the nucleus accumbens (NAc) relies on how the membrane excitability of its principle medium spiny neurons (MSNs) translates excitatory synaptic inputs into action potential firing, while deviated NAc function contributes to drug addiction. Here, we report a synapse-membrane homeostatic crosstalk (SMHC), through which an increase/decrease in excitatory synaptic strength induced a homeostatic decrease/increase in the membrane excitability, and vice versa, resulting in overall functional stability of NAc MSNs. After short-term withdrawal from cocaine self-administration, despite no actual change in excitatory synaptic strength in NAc MSNs, GluN2B NMDA receptors, the SMHC sensors of synaptic strength, were upregulated, creating false signals that induced an SMHC-mediated decrease in membrane excitability. This decreased membrane excitability is partially mediated by increased expression of SK2 type calcium-activated potassium channels. The decreased membrane excitability subsequently induced another SMHC cascade to increase excitatory synaptic strength over long-term cocaine withdrawal through synaptic accumulation of calcium-permeable AMPA receptors. Disrupting the cascading of SMHC-based dysregulation in NAc neurons prevented the progressive intensification of cocaine seeking after drug withdrawal. Thus, cocaine exposure triggers cascades of homeostatic dysregulation to promote progressive intensification of drug seeking after withdrawal.

Disclosures: J. Wang: None. **M. Ishikawa:** None. **M. Otaka:** None. **J.Y. Kim:** None. **G.R. Gardner:** None. **Y.H. Huang:** None. **J.W. Hell:** None. **R.C. Malenka:** None. **M.E. Wolf:** None. **O. Schlüter1:** None. **Y. Dong:** None.

Poster

662. Structural Plasticity: Cellular

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Topic: B.08. Synaptic Plasticity

Title: Integrative morphological analyzes to enhance NMJs diagnostic power

Authors: *S. BARBAT, R. ROBITAILLE
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Abstract: The neuromuscular junction (NMJ) is increasingly pointed out in various models where losses of muscle mass and function are noted. The desire to determine the involvement of NMJs in those phenomena has greatly motivated the development of methods to analyze them. Yet, these morphological analyzes remain superficial and often limited to the organization of the postsynaptic endplate and the level of fragmentation. Yet, NMJs are composed of three main components; AChRs, but also the axon terminal and Perisynaptic Schwann Cells (PSCs; Glial cells covering pre- and post-synaptic elements). Here, we propose a systematic and extensive methodology using all 3 components to study the morphology of NMJs. To test the sensitivity of the method, we compared active and sedentary adult mice (12 months) where changes should be subtle owing to their young age. In each group, 15 soleus were stained for AChRs (α-BTX), axonal terminal (NFM/SV2), and PSCs (S100β). Five soleus were also used to determine the motor unit type by staining for MHCI, MHCIIa and AChRs. At least 20 surface NMJs for each muscle were imaged by confocal microscopy. As expected, NMJs of sedentary mice were more fragmented (4.0±0.1 vs. 2.3±0.1 fragments, $p<0.0001$). However, the innervation status was similar between active and sedentary mice (≈95% innervated, 4% partially denervated and 1% denervated in both groups). Similarly, the coverage of pre and post-synaptic elements by PSCs was similar between active and sedentary mice (≈97% covered, 2% partially covered and 1% not covered in both groups). Yet, more detailed analyzes revealed that sedentary mice had higher proportions of NMJs with ectopic fragments (0.1±0.1% vs. 1.6±0.5%, $p=0.0038$). Interestingly, this was not MHC-type dependent. Furthermore, more terminal (13.5±0.7% vs. 8.8±1.1%, $p=0.0017$) and axonal (6.0±0.8% vs. 3.3±0.8%, $p=0.0190$) sprouting were observed in sedentary compared to active mice. Similarly, more terminal (8.4±1.0% vs. 4.3±0.7%, $p=0.0012$) and axonal (5.7±0.8% vs. 3.3±0.7%, $p=0.036$) glial extension were observed in sedentary compared to active mice. Furthermore, by using *relative risk analyzes* we observed that the interaction between events was influenced by sedentarity. In conclusion, where superficial analyzes failed to reveal differences, more detailed analyzes revealed high level of instability underlying the presence of dynamic mechanisms. Given that changes at the NMJ precede and trigger changes at the muscle (that is, losses of muscle mass and strength), using this method and being able to observe such subtle changes may confer a powerful predictive advantage compared to traditional methods.

Disclosures: **S. Barbat:** None. **R. Robitaille:** None.

Poster

662. Structural Plasticity: Cellular

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant NS20480

Title: Vital imaging of myonuclei

Authors: *R. HASTINGS, W. J. THOMPSON
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Abstract: Skeletal muscle fibers are multinucleate cells generated in early development by the fusion of individual myoblasts. The nuclei initially lie in the center of elongating myotubes but move to the sarcolemma at the periphery of each maturing fiber. When a muscle fiber is damaged, necrosis of the damaged segment is followed by regeneration from satellite cells that migrate to the injury site, differentiate, fuse, and grow to regenerate the muscle fiber. After this regeneration event, the nuclei of the former satellite cells remain, at least temporarily, in the center of the fiber. Therefore, the presence of “central myonuclei” has long been accepted as a marker for a degeneration/regeneration event having occurred in the muscle fiber. It is unclear, however, whether these central myonuclei ever migrate outwards to become peripheral myonuclei. To determine whether central myonuclei migrate to the periphery, I have bred mice possessing a vital transgenic fluorescent label of myonuclei that allows for repeated *in vivo* imaging. I am using these mice to observe damage events in which central myonuclei appear in the muscle fiber, and to observe when and whether those myonuclei subsequently migrate to the periphery of the muscle fiber.

Disclosures: R. Hastings: None. **W.J. Thompson:** None.

Poster

662. Structural Plasticity: Cellular

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Topic: B.08. Synaptic Plasticity

Support: NIH-NS20480

Title: Myofiber development and regeneration in a mouse model of muscular dystrophy

Authors: *R. MASSOPUST, W. THOMPSON
Texas A&M Univ., College Station, TX

Abstract: Duchenne muscular dystrophy (DMD) is an X-linked degenerative muscle disease that affects roughly 1:3,500 males. Caused by frame-shift mutations in the dystrophin gene, dystrophic individuals lack functional dystrophin protein. This dysfunction leads to membrane instability, progressive muscle degeneration, fibrosis, loss of ambulation, and ultimately, premature death. Because diagnosis typically does not occur until 4 years old there is little known about muscle development at early stages of the disease. Muscular dystrophy x-linked (*mdx*) mice are models of DMD and are caused by a homologous mutation. The onset of obvious disease pathology in *mdx* mice occurs between 3 and 8 weeks, depending on the muscle. Over the course of subsequent weeks, the muscle undergoes significant necrosis and repair. During development, myoblasts fuse to form multiple and centrally nucleated myotubes. Nuclei then move from the center to the periphery of the fiber coincident with the formation of myofibrils. After muscle injury such as that occurring in mdx, satellite cells proliferate to form myoblasts. Similar to development, myoblasts line up at the site of damage and fuse to repair the myofiber, leaving behind chains of centrally located nuclei. There is debate regarding whether central nuclei in regenerated myofibers move to the periphery as they do in development. Centrally positioned nuclei after initial development have long been appreciated as a marker of regenerated muscle fibers, but not as a contributor to disease states. In the present work, single myofibers were isolated from 2, 6, 12 and 24 week old *mdx* and wild type (WT) mice. Myofibers were stained with α-bungarotoxin and DAPI, to image acetylcholine receptors (AChRs) and nuclei respectively. Myofibers were reconstructed using confocal microscopy. At 2 weeks of age, before the onset of obvious necrosis, *mdx* myofibers have significantly larger volume and increased myonuclear number relative to age-matched WT fibers. At 12 weeks of age, *mdx* myofibers are hypernucleated and have a significantly higher incidence of central nuclei. By 24 weeks of age, myofibers have significantly larger volume, are hypernucleated and have a higher incidence of central nuclei relative to age-matched controls. These results indicate *mdx* myofibers are developmentally distinct from WT even before the onset of disease pathology.

Disclosures: R. Massopust: None. **W. Thompson:** None.

Poster

662. Structural Plasticity: Cellular

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Topic: B.08. Synaptic Plasticity

Support: NIH-NS20480

Title: Neuromuscular acetylcholine receptor dynamics in dystrophic mice mimic those caused by endogenous muscle injury

Authors: *S. HADDIX[1], W. J. THOMPSON[2]
[1]Inst. for Neurosci., [2]Biol., Texas A&M Univ., College Station, TX

Abstract: Duchenne muscular dystrophy (DMD) is a fatal myopathy that has no cure. There are also abnormalities of the neuromuscular junction (NMJ) in animal models of DMD, which include fragmentation and expansion of the acetylcholine receptor (AChR) endplate, changes in axon morphology, and an increased number of terminal Schwann cells. The remodeling is likely initiated by muscle fiber necrosis and regeneration at the junction. To investigate the events underlying the restructuring of dystrophic NMJs, we utilize a technique to visualize the dynamics of AChRs in *mdx* mice, a murine model of DMD. A low concentration of bungarotoxin (BTX) conjugated to a fluorophore is applied to the sternomastoid muscle of an *mdx* mouse to label junctions *in vivo*. Following a 10-day recovery period, which allows for natural myofiber degeneration and regeneration and receptor turnover, the animal is sacrificed and labeled with BTX conjugated to a different fluorophore. We hypothesize that if a necrotic event occurs at the endplate region during the 10-day period the first color BTX will be lost or remodeled. The second color BTX will stain robustly, as receptors must be inserted into the sarcolemma for transmission to resume or as a result of the ongoing AChR turnover. In control animals the first and second BTX applications label the same population of receptors and show no difference in morphology. These we interpret to be fibers that have not undergone a necrotic event at the junction during the 10-day interval. However, in a significant number of the *mdx* synapses the first color BTX has mostly disappeared and the second color of BTX labels a fragmented endplate. We term these dynamic junctions. We show here that receptor turnover is higher in dystrophic muscles, corresponds to synaptic remodeling and suggest that the cause of increased receptor dynamics is necrosis and subsequent regeneration of the muscle fiber at the endplate region. Indeed these endplates are similar to the endplates in two models of muscle injury. The proportion of dynamic junctions is elevated and constant in *mdx* mice from P38 to P450. Our results indicate that muscle fiber degeneration and regeneration is occurring at a consistent rate well beyond the proposed “crisis” period and contributes to synaptic remodeling in dystrophy. Additionally, when tension recordings are made from the sternomastoid muscles of P160 animals, preliminary evidence shows discrepancies in neuromuscular transmission suggesting that this turnover and remodeling has functional repercussions.

Disclosures: S. Haddix: None. **W.J. Thompson:** None.

Poster

662. Structural Plasticity: Cellular

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Topic: B.08. Synaptic Plasticity

Support: NIH 20480

Title: Difference in the timing of neuromuscular synapse elimination correlates with properties of target muscle fibers

Authors: *Y. LEE[1], W. J. THOMPSON[2]
[1]Dept. of Biol., [2]Biol., Texas A&M Univ., College Station, TX

Abstract: The emergence of a mature nervous system requires a significant refinement of synaptic connections and neuronal networks initially formed during development. Such refinement includes elimination and remodeling of existing synapses, commonly termed "synapse elimination," and occurs throughout the nervous system. Similar synaptic remodeling also occurs during aging, in disease and throughout life providing cellular basis for learning and memory. The process of developmental synapse elimination is most extensively studied at the rodent neuromuscular junction (NMJ). At a mature NMJ, high-density aggregates of the postsynaptic acetylcholine receptors (AChR) are each apposed by presynaptic terminals of a single motor neuron, and the processes of terminal Schwann cells (tSCs; glia of the NMJ) cap the synaptic apposition. During early postnatal development, each of up to ~10 motor axons that converge onto a postsynaptic muscle fiber; these inputs are removed until each NMJ is innervated by a single motor neuron. Previous studies, including our own, have demonstrated that neuronal activity as well as behaviors of synaptic glia influence the course of synapse elimination. It is, however, unclear whether target muscle fibers are more than naïve substrates for innervation but rather are active participants in removal of redundant axonal inputs. I present evidence that the rate at which synapse elimination proceeds depends, at least partly, on the contractile property (fast vs. slow) of the target muscle fiber on which the synapse is situated. Thus, the results indicate that postsynaptic muscle fibers, whose contractile properties are matched with the activity patterns of the innervating motor neurons, likely also provide instructive cues that affect the outcome of local synapse elimination.

Disclosures: Y. Lee: None. **W.J. Thompson:** None.

Poster

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Topic: B.08. Synaptic Plasticity

Support: NIGMS R25-GM061838

NIGMS R25-GM06115115

Title: Cortactin expression is driven by wingless and neuronal activity to allow synaptic plasticity at the *Drosophila* neuromuscular junction

Authors: *C. M. DOMINICCI-COTTO[1], M. PEREZ CARAMBOT[2], C. MALDONADO[3], B. MARIE[4]
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Abstract: Wingless (Wg), a major signaling molecule, is essential for the plasticity of the nervous system. Recently, it was shown that the Drosophila neuromuscular junction (NMJ) serves as a model to understand the molecular mechanisms underlying activity-dependent synaptic plasticity. Upon repeated stimulations, the NMJ undergoes modifications in synaptic structure (apparition of de-novo synaptic boutons) which are dependent on the Wg signaling pathway. Still, little is known about the cytoskeletal changes or molecular components controlled by Wg that allow this plasticity. Here, we focus on how the actin regulator Cortactin (Cttn) is related to this process. Using genetics and confocal microscopy, we assess the role of Cttn in regulating activity-dependent synaptic plasticity. We show that Cttn is present at the NMJ pre- and post-synaptically and that de-novo synaptic structures related to synaptic plasticity are dependent on pre-synaptic Cttn. Indeed, these synaptic structures that appear after high neuronal activity contain Cttn at an early stage of their formation. In addition, we show that Cttn protein levels increase after repeated stimulations and that this increase is required for activity-dependent plasticity. To strengthen these results, we blocked action potentials and neurotransmitter release with the use of paralytic (para) and synaptotagmin (syt) mutants respectively. After repeated stimulations, there is no increase of Cttn and no plasticity in para and syt mutants, thus neuronal activity is required for the increase of Cttn and synaptic plasticity. Lastly, since the Wg pathway is required for activity-dependent synaptic plasticity, we tested wether the increase in Cttn after stimulation is also dependent on this pathway. To do so, we asked whether Cttn intensity was affected in Wg mutant larvae and frizzled (fz2) RNAi transgenic larvae (Fz2 is the Wg pre-synaptic receptor). We found that Cttn is not increased after stimulation in both Wg and fz2 deficient larvae and that plasticity is also impaired. This suggests that the pre-synaptic Wg signaling is required for the increase of Cttn and for plasticity. Overall our results strongly suggest that during repeated stimulation the expression of Cttn is required for the regulation of synaptic plasticity under the control of Wg signaling.

Disclosures: C.M. Dominicci-Cotto: None. **M. Perez Carambot:** None. **C. Maldonado:** None. **B. Marie:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.07/H12

Topic: B.08. Synaptic Plasticity

Support: NIH NIGMS R25GM06115115

NIH NIGMS 1P20GM103642

NIH NIMHD 8G12-MD007600

NIH NIGMS R25GM061838

Title: Cortactin controls electrophysiological properties during activity-dependent synaptic plasticity at the *Drosophila* larva neuromuscular junction

Authors: *C. MALDONADO[1], M. PEREZ[1], C. DOMINICCI[1], B. MARIE[2]
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Abstract: In the nervous system, changes in activity lead to modifications in synaptic structure and function. This phenomenon is referred to as synaptic plasticity and is thought to be the basis of learning and memory. Such changes can be studied at the *Drosophila* neuromuscular junction (NMJ) where we can address the molecular mechanisms underlying activity-dependent synaptic plasticity. Recent work has shown that, after repeated stimulations, *de novo* synaptic structures form at the NMJ while an increase in the frequency of spontaneous release occurs. The secreted molecule Wingless (Wg)/Wnt is known to underlie the structural and electrophysiological changes during activity-dependent plasticity at the NMJ. However, little is known about how this signal mediates the cellular changes that lead to plasticity. In this work, we investigate the role of the actin regulator Cortactin (Cttn) in activity-dependent synaptic plasticity. With confocal microscopy, we show that the synaptic structures that are formed during synaptic plasticity are dependent on presynaptic Cttn expression. In turn, we focused on the functional modifications to the synapses. Through intracellular electrophysiological recordings of the larva NMJ, we show that Cttn-deficient synapses have a significant reduction in the frequency of spontaneous release. Such reduction can only be rescued by the presynaptic expression of Cttn, which suggests that the neuronal expression of Cttn is necessary for maintaining the rate of spontaneous vesicle fusion at the NMJ. Interestingly, Cttn seems to be important for the potentiation of spontaneous release that occurs after activity-dependent synaptic plasticity. Indeed, there is no potentiation of spontaneous release in Cttn mutants and in NMJs depleted of presynaptic Cttn. However, this potentiation is achieved if Cttn is expressed presynaptically in Cttn mutants, or if Cttn is

removed only postsynaptically. It is likely then, that Cttn is responsible for presynaptic functional changes after activity-dependent synaptic plasticity. Overall, our findings suggest that Cttn is an important regulator of structural and physiological properties of the synapse in response to activity.

Disclosures: C. Maldonado: None. **M. Perez:** None. **C. Dominicci:** None. **B. Marie:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.08/I1

Topic: B.08. Synaptic Plasticity

Support: MEXT Japan Grant 17K07041

Title: Genetic interaction of DISC1 and Neurexin in the development of fruit fly glutamatergic synapses

Authors: *K. FURUKUBO-TOKUNAGA[1], H. PANDEY[2], K. BOURAHMOUNE[2], K. KURITA[2], A. SAWA[3]
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Abstract: Originally identified at the breakpoint of a chromosome (1;11)(q42.1; q14.3) translocation in a Scottish family, DISC1 is a highly potent susceptibility gene for various mental disorders. To study neurodevelopmental functions of DISC1 in a genetically tractable model, we have examined functional interactions of *DISC1* and other risk factor genes using the fruit fly (*Drosophila melanogaster*). Here, we show that DISC1 interacts with *dnrx1*, the *Drosophila* homolog of the human neurexin (NRXN1) gene, in the development of glutamatergic synapses. We show that reduction of *dnrx1* activity abolished DISC1-mediated suppression of synaptic bouton areas while DISC1 caused suppression of axonal terminal branching in both *dnrx1* mutant and RNAi background. Reduction of *dnrx1* also suppressed DISC1-mediated stimulation of active zone density and upregulation of the expression of Bruchpilot, a *Drosophila* ELKS/CAST protein, in presynaptic motoneurons. Reduction of *dnrx1* activity also modified DISC1 overexpression phenotypes in postsynaptic cells. Thus overexpression of DISC1 in wild-type background stimulated the expression of DGluRIIA but failed to do so in the *dnrx1* heterozygous background. Moreover, overexpression of DISC1 in the *dnrx1* heterozygous background caused mislocalization of Disc-large, the *Drosophila* PSD-95 homolog. We further show that overexpression of DISC1 in pre- but not postsynaptic cells suppressed the DNRX1 expression in the synaptic boutons. Analyses with a series of DISC1 domain deletion constructs have revealed that axodendritic localization of DISC1 is crucial for efficient suppression of

DNRX1. These results thus suggest an intriguing converging mechanism controlled by the interaction of neurexin and DISC1 in the developing glutamatergic synapses.

Disclosures: K. Furukubo-Tokunaga: None. **H. Pandey:** None. **K. Bourahmoune:** None. **K. Kurita:** None. **A. Sawa:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.09/I2

Topic: B.08. Synaptic Plasticity

Support: Motor Neurone Disease Research Institute Australia

Dianne Eerden Elite Top-Up Living Allowance Scholarship Award

Title: The alterations of neurite outgrowth and synapse development in tdp-43^{A315T} primary cortical neurons

Authors: *T. JIANG, M. BRIZUELA, E. HANDLEY, E. DAWKINS, T. DICKSON, C. BLIZZARD
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Abstract: Neurite outgrowth alterations and synapse dysfunction have been implicated in models of Amyotrophic lateral sclerosis (ALS). The mislocalisation and/or the mutation of the RNA binding protein TDP-43 are a frequent occurrence in ALS pathogenesis. Recent research indicates that RNA binding protein may play an important role at the neuronal synapse, however the early pathophysiological dysfunctions causing impairment in synapse are still unknown. Here we utilized the prpTDP-43^{A315T} : YFP mouse model expressing human mutant TDP-43 (TDP-43^{A315T}) in cortical motor neurons to investigate the influence of TDP-43^{A315T} on neurite structure and synapse formation. Primary cortical neurons, derived from individual E15.5 embryos were grown to 3, 5, 10 and 15 days in vitro (DIV). In primary cortical neurons TDP-43^{A315T} expression was localized to both the nucleus and cytoplasms. Our data implicated that there was a significant difference between wild type (WT) and TDP-43^{A315T} primary cortical neurons in total dendrite length, mean length at 15 DIV, with no effect on dendrite complexity. Using YFP positive WT and TDP-43^{A315T} cortical neurons we demonstrated a significant decrease in dendritic spines density in the TDP-43^{A315T} cortical neurons in comparison to WT controls at both 10 and 15 DIV. Furthermore, we discovered that axonal growth cone dynamics and growth cone pausing and extension was significantly altered by overexpression of TDP-43^{A315T} and whilst there was no change in axonal outgrowth and growth cone areas. This work indicates TDP-43^{A315T} mutation may play a role in the formation of synaptic structures and

function in cortical neurons. Unravelling the mechanisms that render neurons in the cortico-motor system vulnerable to TDP-43 misprocessing and pathology will be imperative in the pursuit of identifying novel therapeutic interventions.

Disclosures: **T. Jiang:** None. **M. Brizuela:** None. **E. Handley:** None. **E. Dawkins:** None. **T. Dickson:** None. **C. Blizzard:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.10/I3

Topic: B.08. Synaptic Plasticity

Support: CIHR

Title: Excessive lysosomal degradation induced by the Christianson Syndrome mutation NHE6 ΔES impairs AMPA receptor trafficking and structural plasticity in hippocampal neurons

Authors: *A. Y. GAO[1], A. ILIE[2], J. ORLOWSKI[2], R. A. MCKINNEY[3]
[1]Integrated Program in Neurosci., [2]Physiol., [3]Pharmacol. & Therapeut., McGill Univ., Montreal, QC, Canada

Abstract: Proper endosomal trafficking is important for neuronal morphology and plasticity, and deficits in this process have recently been implicated in a number of neurological disorders. This includes Christianson Syndrome (CS), an X-linked neurodevelopmental disorder characterized by intellectual disability, epilepsy, ataxia, and autistic features. Although CS is believed to be one of the most common forms of X-linked intellectual disability worldwide, little is known of its underlying etiology, and intervention for affected individuals is thus lacking. CS is due to mutations in the *Slc9a6* gene encoding intracellular sodium/proton exchanger NHE6, which localizes to early and recycling endosomes and regulates their luminal pH. We were the first to show that in hippocampal neurons, NHE6 colocalizes with a subset of AMPA receptors (AMPARs) and is recruited to excitatory synapses following chemical long-term potentiation (LTP). However, the impact of clinical mutations in NHE6 upon neuronal structure and function have not yet been studied. To this end, we are investigating a prevalent NHE6 loss-of-function mutation with deletions of amino acids Glu287 and Ser288 (NHE6 ΔES). Sparse transfection of NHE6 ΔES into primary hippocampal neurons decreased dendritic branching and mature dendritic spine density. Moreover, NHE6 ΔES showed reduced colocalization with early and recycling endosomal markers, yet greater colocalization with markers for late endosomes and lysosomes, which implied an excessive degree of lysosomal degradation. To investigate how this could impact receptor trafficking, we then assessed the localization of tropomysin receptor kinase B (TrkB), the high-affinity receptor for brain-derived neurotrophic factor (TrkB). While

overall levels of TrkB were comparable, there was a significant attenuation in active phosphorylated TrkB in NHE6 ΔES-transfected cells. This suggested an impairment in BDNF/TrkB signaling, which is crucial for proper spine formation and maturation. Furthermore, NHE6 ΔES expression prevented spine enlargement and AMPAR insertion into synaptic sites following LTP, indicating an impairment in cellular learning mechanisms. However, applying inhibitors of lysosomal degradation to NHE6 ΔES-expressing neurons partially rescued their deficits in dendritic spine density, AMPAR trafficking, and the structural response to LTP. Overall, we find that NHE6 ΔES disrupts the structure and remodeling of hippocampal pyramidal neurons, which may be the cause of learning and memory impairments in CS patients.
Funding: CIHR.

Disclosures: **A.Y. Gao:** None. **A. Ilie:** None. **J. Orlowski:** None. **R.A. McKinney:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.11/I4

Topic: B.08. Synaptic Plasticity

Support: Hussman Foundation HIAS15003

Title: Autism-associated mutation of syntaxin binding protein 5 disrupts dendritic morphology

Authors: *W. SHEN, Y.-C. LIN
Hussman Inst. For Autism, Baltimore, MD

Abstract: Autism is a neurological condition that features marked qualitative differences in communication and social interaction. Genetic studies have implicated numerous risk genes, many of which encode proteins important for synaptic development and function and may contribute to autism phenotypic diversity. Deletions and mutations of syntaxin binding protein 5 (STXBP5, also known as tomosyn) are identified in some individuals with autism. STXBP5/tomosyn is a syntaxin binding protein that contains a WD40 domain at the N-terminus and a SNARE motif at the C- terminus. STXBP5/tomosyn has a presynaptic role that negatively regulates neurotransmitter release by forming syntaxin-1-SNAP25-tomosyn complex. STXBP5/tomosyn has also been shown to regulate neurite outgrowth in immature neurons. The WD40 domain has a scaffolding function harboring molecules necessary for signal transduction and vesicle trafficking. Interestingly, two autism-associated variants of STXBP5 exhibit missense mutations at the WD40 domain. Whereas the crucial role of STXBP5/tomosyn in presynaptic terminals has been defined in detail, little is known about its postsynaptic role in dendritic integrity and synaptic strength. Here, we test the hypothesis that the autism-associated STXBP5/tomosyn mutant disrupts dendritic morphology by altering the regulation of dendritic

exocytosis.
To test this hypothesis, the subcellular localization of wildtype (WT) and mutant STXBP5/tomosyn in cultured hippocampal neurons was determined. WT- and mutant tomosyn was found to all localize to axons, dendrites and dendritic spines. Knockdown of STXBP5/tomosyn in cultured neurons reduced dendrite arborization, soma size, and dendritic spine density, but the expression of the mutant tomosyn protein failed to rescue the reduced spine density in tomosyn knockdown neurons. Moreover, the mutant tomosyn altered its binding to syntaxin-4, a postsynaptic t-SNARE protein involved in glutamatergic receptor trafficking, potentially leading to disruption of dendritic integrity and synaptic strength.
In conclusion, STXBP5/tomosyn plays an important role in regulating dendritic morphology. Mutations of *STXBP5* found in individuals with autism may alter structural and functional plasticity of dendritic spines, and potentially disrupt normal developmental processes in brain formation.

Disclosures: **W. Shen:** None. **Y. Lin:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.12/I5

Topic: B.08. Synaptic Plasticity

Support: T32GM007753

T32MH020017

Harvard-MIT Health Sciences & Technology (HST) IDEA2 Award

Harvard Sackler Fellowship in Psychobiology

Stanley Center for Psychiatric Research, Broad Institute of MIT & Harvard

Title: Schizophrenia risk from a negative-regulator of synaptic pruning

Authors: ***M. L. BAUM**[1,2,3,4,5], S. DE BOER[6,2,7], H. DE RIVERA[3,2], G. GENOVESE[2,3], N. KAMITAKI[3,2], D. A. SABATINI[8,1], W. WANG[9], D. HAZELBAKER[2], D. VARGAS[1], J. PRESUMEY[10], B. HAVIK[11], M. C. CARROLL[10], B. L. SABATINI[9], L. E. BARRETT[2,6], K. EGGAN[6,7,2], S. MCCARROLL[3,2], B. A. STEVENS[1,2]
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Mol. and Cell. Biol., Cambridge, MA; [8]Univ. of Chicago, Chicago, IL; [9]Harvard Med. Sch. Dept. of Neurobio., Boston, MA; [10]Boston Children's Hosp. Program in Cell. and Mol. Med., Boston, MA; [11]Univ. of Bergen Dept. of Clin. Sci., Bergen, Norway

Abstract: The unmet clinical need of those suffering from mental illness is staggering, with Schizophrenia alone accounting for 16.8 million Disability Adjusted Life Years (DALYs) globally. There is urgent need, consequently, to better understand the molecular mechanisms important in the pathogenesis of schizophrenia. Aberrant developmental pruning of synapses may be one important mechanism contributing to schizophrenia risk; we showed that increasing gene-dosage of Complement Component 4 (C4) increased schizophrenia risk and that loss of C4 in a mouse abrogated normal synaptic refinement in the developing visual system. From this previous work, we hypothesized that there might also be an endogenous negative-regulator of this pruning machinery hypofunction of which might also lead to over-pruning in a way that would contribute to schizophrenia risk. We conducted an in depth inquiry into whether such a negative regulator of pruning could be encoded by the giant gene, CSMD1 (CUB and Sushi Multiple Domains 1), which is robustly associated with schizophrenia risk through recent genome-wide association studies (GWAS). CSMD1 is a ~ 2Mb gene on chromosome 8 that encodes a brain-enriched, large type-I transmembrane protein. Both of the protein interaction domains, CUB and Sushi domains, are present in known regulators of complement and a previously published in vitro study has shown that small fragments of CSMD1 can bind and act as a cofactor for degradation of multiple members of the complement cascade, including C4. Despite these intriguing findings, very little is known about the normal functions of CSMD1 in the brain and how variation in the gene contributes to schizophrenia risk. Using a csmd1 KO mouse and a human embryonic stem cell line with biallelic frame-shifting deletions in CSMD1, we present here the first evidence that CSMD1 has a role in vivo and in human neural cells in regulating complement activation, synapse number, and functional biomarkers of pruning. Our preliminary data show that loss of Csmd1 leads to enhanced complement fixation over-refinement of the developing mouse retinogeniculate system, and that pruning-relevant dysfunction extends beyond the visual system in mice. Our preliminary findings show that disruptions to complement biology extend as well to human embryonic stem cell derived NGN2-positive neurons lacking CSMD1. Though many questions remain, this poster presents the first evidence for a role of CSMD1 in regulating synapse number and complement in the murine brain and human neural tissues, and suggests

Disclosures: M.L. Baum: None. **S. de Boer:** None. **H. de Rivera:** None. **G. Genovese:** None. **N. Kamitaki:** None. **D.A. Sabatini:** None. **W. Wang:** None. **D. Hazelbaker:** None. **D. Vargas:** None. **J. Presumey:** None. **B. Havik:** None. **M.C. Carroll:** None. **B.L. Sabatini:** None. **L.E. Barrett:** None. **K. Eggan:** None. **S. McCarroll:** None. **B.A. Stevens:** F. Consulting Fees (e.g., advisory boards); Annexon Scientific Advisory Board.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.13/I6

Topic: B.08. Synaptic Plasticity

Support: MOST Grant MOST 105-2628-B-038 -005 -MY3

Title: CCL5 regulating synaptogenesis promotes memory formation

Authors: *S.-Y. CHOU[1], R. AJOY[1], B. J. HOFFER[2], Y.-H. CHEN[3]
[1]Grad. Inst. of Neural Regenerative Med., Taipei Med. Univ., Taipei, Taiwan; [2]Scientist Emeritus, NIDA/NIH, Lyndhurst, OH; [3]Tri-Service Gen. Hospital/National Def. Medi, Taipei City, Taiwan

Abstract: Introduction - CCL5 belongs to CC chemokine family and locates in chromosome 17 in humans. Previous studies have identified that CCL5 releasing from astrocyte promotes neurite outgrowth and neuronal activity. CCL5 responses for Hepatocyte Growth Factor (HGF) mediated axon outgrowth and branching which linking CCL5 to axon morphogenesis. Also, lower serum level of CCL5 was found in Alzheimer's disease (AD) patients. Some studies suggest that CCL5 protects the neurons from the damaging effects of Aβ deposits and could be an reitical factor in AD stem cell therapy. However, the mechanism of CCL5 in memory and neuronal function remains unclear. In the current study, we investigate the contribution and mechanism of CCL5 in mouse memory performance with a CCL5 knockout mouse (CCL5-/-). Methods - Novel Object Recognition Test, Object Location Test, stereotactic surgery, Western Blot for protein analysis, Synapsosome purification (for the isolation of synaptic proteins), cell culture, Immunostaining, and EPSP test. Results - The results showed that mice lacking of CCL5 performed impaired memory in both object recognition/location tests and hippocampal neuron electroactivity as EPSP. The performance on behavioral tasks and hippocampal neuron EPSP was improved when re-introducing CCL5/RANTES into the hippocampal region of the CCL5-/- mice. Protein analysis found increased synaptic-related proteins - PSD 95, Synaptophysin and GAP43 in hippocampus regions by CCL5/RANTES administration. Further cellular studies we identified CCL5 activates PI3K and increases mitochondria synaptic movement which promotes synaptogenesis. Conclusions - CCL5 plays a vital role in memory formation through its ability to enhance the Mitochondrial responded synaptogenesis.

Disclosures: **S. Chou:** None. **R. Ajoy:** None. **B.J. Hoffer:** None. **Y. Chen:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.14/I7

Topic: B.08. Synaptic Plasticity

Support: NINDS intramural funds

Title: Activity-dependent structural changes in subsurface cisterns of hippocampal neurons

Authors: *J.-H. TAO-CHENG
NINDS, NIH, Bethesda, MD

Abstract: Subsurface cistern (SSC) is a specialized compartment of the endoplasmic reticulum (ER) in neuronal soma and primary dendrites that is in close apposition (~10 nm) to the plasma membrane (PM). Such ER-PM close appositions (called “ER-PM contact sites”) are involved in intracellular calcium regulation. Here, structural changes of SSC in hippocampal neurons were examined by electron microscopy upon depolarization with high K^+ or treatment with NMDA. In both experimental systems (10-14 day old organotypic hippocampal slice cultures and 3 week old dissociated hippocampal cultures), the number of SSC-PM contact sites in neuronal somas significantly decreased under these excitatory conditions. In hippocampal slice cultures, the number of SSC in pyramidal cells of the CA1 region decreased to ~40% of control levels after 1 min of high K^+ (90 mM, 2 exp), and to ~ 50% after 1 min of NMDA (50 µM, 2 exp) treatment. In dissociated hippocampal cultures, the number of SSC decreased to ~55% of control levels after 2 min of high K^+ (3 exp), and to ~ 65% after 2-3 min of NMDA (2 exp) treatment. Furthermore, in dissociated neuronal cultures, the average length of the SSC-PM contact area significantly decreased to ~ 60% of control values upon depolarization or NMDA treatment. This decrease in SSC-PM apposition was reversible 30 min after the cessation of treatment in both experimental systems. These results demonstrate a structural decoupling between the SSC and the PM upon stimulation, suggesting that there may be a functional decoupling of the calcium regulation. Because SSC-PM contact sites mediate calcium influx, the decrease in contact area may protect neurons from calcium overload upon intense stimulation.

Disclosures: J. Tao-Cheng: None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.15/DP02/I8 (Dynamic Poster)

Topic: B.09. Physiological Properties of Neurons

Title: TMEM24, a lipid transporter at ER-plasma membrane contacts enriched in neurons and regulated by calcium

Authors: *M. MESSA[1], E. W. SUN[2], P. V. DE CAMILLI[3,4]
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Abstract: The endoplasmic reticulum (ER) is a sub-cellular compartment with a multiplicity of functions, including synthesis of most membrane lipids. The ER is functionally interconnected to most other cellular membranes via vesicular transport. In addition, it forms juxtapositions (10-30nm distance) with other membranes, including the plasma membrane (PM), via protein tethers. Some of these tethers contain lipid transport modules and mediate lipid exchange between the two adjacent bilayers, independently of fusion and fission reactions. Several such tethers have been identified and characterized, but the full picture is far from complete. TMEM24, an integral membrane protein of the ER predominantly expressed in neurons and neuroendocrine cells, functions as a tether between the ER and the PM. It comprises in sequence an N-terminal transmembrane region, an SMP domain (a module that transports glycerolipids), a C2 domain and a polybasic, unstructured C-terminal region that binds the PM in trans. We have previously shown that in pancreatic ß-cells the membrane tethering properties of TMEM24, which are required for its lipid transport function, are regulated by cytosolic Ca^{2+} via the interplay of protein kinase C and calcineurin (1). We have additionally provided evidence for a role of TMEM24 in insulinoma cells in the control of pulsatile Ca^{2+} elevations, suggesting feed-back loops between lipid transport and the dynamics of Ca^{2+} required for secretion (1). Here we have begun to explore the function of TMEM24 in the nervous system. TMEM24 is preferentially enriched in neurons versus glial cells and its expression in neuronal cells correlates with neuronal differentiation and maturation. Transfected TMEM24-EGFP localizes at neuronal ER-PM contacts at rest, but is shed from these contacts and rapidly redistributes throughout the entire ER upon experimental manipulations that result in elevation of cytosolic Ca^{2+}. These include trains of electric stimulation, K^+ depolarization, NMDA stimulation and Ca^{2+} uncaging. A similar concentration at ER-PM contract sites at rest is observed in gene edited neuroblastoma cells expressing EGFP-tagged TMEM24 at endogenous levels. We are currently further investigating the dynamics of TMEM24 and its role in neuronal function.
1. Lees, J. A., Messa, M., et al. (2017). Lipid transport by TMEM24 at ER-plasma membrane

contacts regulates pulsatile insulin secretion. Science (New York, NY), 355(6326), eaah6171. http://doi.org/10.1126/science.aah6171

Disclosures: **M. Messa:** None. **E.W. Sun:** None. **P.V. De Camilli:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

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Program#/Poster#: 662.16/I9

Topic: B.08. Synaptic Plasticity

Support: Wellcome Trust PhD Studentship

Medical Research Council Grant MR/J013188/1

EUFP17 Marie Curie Actions Grant PCIG10-GA-2011-303680

UK MRC, BBSRC and EPSRC Grant MR/K01580X/1

Title: *In vivo* imaging of mitochondrial localisation during structural synaptic plasticity

Authors: *R. M. LEES[1], J. D. JOHNSON[1], L. M. COLLINSON[3], P. VERKADE[2], M. C. ASHBY[1]
[1]Ctr. for Synaptic Plasticity, Sch. of Physiology, Pharmacol. and Neuroscie, [2]Univ. of Bristol, Bristol, United Kingdom; [3]The Francis Crick Inst., London, United Kingdom

Abstract: Most synapses in the adult mammalian cortex are assumed to persist for the entire lifetime of the animal. However, a small but significant population are transient, continually being formed and eliminated. This process of structural synaptic plasticity is thought to modify connectivity within cortical circuits during learning and memory formation. Mitochondria are found at a subset of presynaptic terminals where they can modulate neurotransmission through calcium sequestration and adenosine triphosphate (ATP) provision. While it is thought that mitochondria are essential for synaptic function, it is not known whether they are required for the persistence of presynaptic terminals. In particular, whether the recruitment of resident mitochondria relates to the long-term stability of a presynaptic terminal.
To answer these questions, in vivo two-photon imaging was used to track mitochondrial and synaptic localisation over short (<4 days) and long (>30 days) time periods. A bicistronic AAV1/2 was used to express cytosolic enhanced green fluorescent protein (EGFP) and mitochondrially-targeted red fluorescent protein (mito-tagRFP) in pyramidal neurons of the primary motor cortex. A cranial window was implanted over the somatosensory cortex to allow repeated imaging of the structure and mitochondrial content of projecting axons and their presynaptic boutons over time.

Mitochondria were found to be more stably localised to synaptic sites than non-synaptic sites. The initial recruitment of mitochondria to newly formed presynaptic terminals was related to the stabilisation of those synapses. The profile of mitochondrial localisation at pre-existing stable synaptic sites was also analysed to reveal the influence of mitochondrial recruitment on their longevity.
Mitochondrial function and localisation has been linked to synaptic function, and dysregulation of mitochondrial dynamics is linked to many neurodegenerative and neurological diseases. Therefore, the relationship between mitochondrial recruitment and reconfiguration of synaptic connectivity could provide understanding of the dynamics of neuronal and circuit plasticity, leading to a basis for mechanistic intervention.

Disclosures: R.M. Lees: None. **J.D. Johnson:** None. **L.M. Collinson:** None. **P. Verkade:** None. **M.C. Ashby:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.17/I10

Topic: B.08. Synaptic Plasticity

Support: NINDS intramural funding

Title: Neurolastin, a brain-specific dynamin-family gtpase, modulates mitochondrial dynamics

Authors: *R. M. LOMASH[1], R. S. PETRALIA[2], M. C. TSUDA[3], Y.-X. WANG[4], R. YOULE[1], H. A. CAMERON[5], K. ROCHE[1]
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Abstract: Neurolastin is a recently discovered member of the dynamin-family of GTPases. It is a brain-specific protein with both GTPase and E3 ligase activities and shows a cytosolic and endosomal localization. Neurolastin plays an important role in synaptic transmission as its absence *in vivo* leads to fewer dendritic spines, lesser functional synapses, reduced paired pulse facilitation and smaller sized endosomes. We have now found that neurolastin in steady state is partially localized to the mitochondria as well. We have determined that the N-terminus of neurolastin contains a mitochondrial targeting sequence and the protein is being imported into the mitochondrial intermembrane space. By expressing multiple truncations and mutations of neurolastin in HeLa cells and neurons, we observe that inactivation or deletion of the RING domain alters the localization of the protein and leads to a near complete mitochondrial localization, whereas inactivation of the GTPase domain has no effect on localization.

Subsequently, we compared the mitochondrial morphology between wild-type and neurolastin knockout animals in cerebellar Purkinje cells by electron microscopy. We find that the mitochondria in the knockout are more abundant with smaller area and feret diameter, consistent with more fragmented mitochondria. Additionally, we observe that expression of inactive mutants of the GTPase domain leads to more fragmented mitochondria in HeLa cells. We also find that the neurolastin knockout has fewer PCNA positive and DCX positive cells in the adult dentate gyrus suggesting involvement of neurolastin in neurogenesis. Thus, we find that neurolastin is imported into the mitochondrial intermembrane space and regulates mitochondrial membrane dynamics and adult neurogenesis.

Disclosures: R.M. Lomash: None. **R.S. Petralia:** None. **M.C. Tsuda:** None. **Y. Wang:** None. **R. Youle:** None. **H.A. Cameron:** None. **K. Roche:** None.

Poster

662. Structural Plasticity: Cellular

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 662.18/J1

Topic: B.08. Synaptic Plasticity

Support: NIH RO1-EY011894

JBP Foundation

Title: Activity-dependent excitatory synapse stabilization in mouse visual cortex

Authors: *K. MICHEL, J. SUBRAMANIAN, M. R. BENOIT, E. NEDIVI
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Abstract: Experience-dependent plasticity drives cortical networks to adapt to environmental changes, allowing appropriate reaction to sensory stimulation throughout life. In mature neuronal networks, plasticity occurs mainly at the synaptic level by forming new synapses and eliminating pre-existing ones. Multiple steps are required for excitatory synapse initiation, stabilization and maturation; however, it has been difficult to delineate the sequence of these events *in vivo* and identify which ones are influenced by activity due to the difficulty of independently labeling and simultaneously tracking dendritic spines and synaptic proteins at high temporal resolution.
To gain insight into the molecular mechanisms that connect sensory stimulation with the selective stabilization of new dendritic spines, we analyzed the role of the activity regulated gene *cpg15* during excitatory synapse stabilization in the visual cortex. By using *in vivo* multi-color two-photon microscopy, we resolved the daily and weekly dynamics of dendritic spines and the postsynaptic scaffolding molecule PSD95 in *cpg15* knockout (KO) mice. CPG15 is a small extracellular molecule whose expression in the cortex is spatially and temporally correlated with

periods of synapse formation and activity dependent plasticity, and can be induced in response to sensory experience. In CPG15 KO mice we found a similar rate of spine initiation compared to wild type mice, however fewer of these new spines were able to recruit PSD95 and stabilize. This difference in spine stabilization was only apparent with normal visual experience, suggesting CPG15's function in synapse stabilization is indeed coupled to sensory stimulation. CPG15 is a component of the AMPA receptor proteome and its expression can promote synapse maturation through the incorporation of AMPA receptors into the postsynaptic membrane. By investigating CPG15's interaction with AMPA receptors and its functional relevance to cortical plasticity, we propose a novel mechanism for the selective stabilization of excitatory synapses in response to sensory stimulation.

Disclosures: K. Michel: None. **J. Subramanian:** None. **M.R. Benoit:** None. **E. Nedivi:** None.

Poster

662. Structural Plasticity: Cellular

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Topic: B.08. Synaptic Plasticity

Support: CNS Foundation 31601145

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CSC scholarship

Title: Modulation of Neurofilament kinetics and axonal morphology near excavation of mouse optic nerve

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Abstract: Neurons send signals out to target neurons via action potentials propagating along axons, and the rate of which is proportional to the diameter of axonal caliber. Axon is comprised of three typical cytoskeletal proteins, neurofilaments (NFs) are the most abundant filaments, which mainly determine the axonal morphology. After synthesized in the cell body, NFs are continuously shipped out by molecular motors along microtubule tracks by a 'stop and go' manner, which is called "Slow Axonal Transport" by the slow average velocity of 0.1-3 mm/day. The "Slow Axonal Transport" of NFs has been mathematically described by the '6-state' model. In the model, NFs can alternate between on-track running, on-track short term pausing (with seconds to minutes) and off-track long term pausing (with hours) states in both anterograde and retrograde directions. The probability of NFs transit from one state to another is determined by

specific transition rates, which can be observed from experiments. Near the excavation region of mouse optic nerve, the number of NFs has doubled around 100 and 150 micron meter, and further increased to a total of threefold at 1200 micron meter, as observed by experiments. We hypothesize that the Conservation Law in physics provides a fundamental principle to dissect the relationship between NF kinetics and morphology of axons. The modification of on-track rate can successfully reproduce the population distribution of NFs, and it gives a prediction on the changes of NFs kinetic properties through this excavation region. Biophysically, the on-track rate is correlated closely with the cytoskeletal composition, especially the variation of ratios of microtubules to neurofilaments along this excavation area.

Disclosures: Y. Li: None. **A. Brown:** None. **P. Jung:** None.

Poster

662. Structural Plasticity: Cellular

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Support: R21MH098138

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R01DC009809

Title: Neural cell adhesion molecule NCAM regulates perisomatic synapse remodeling and inhibition of pyramidal cells in the developing mouse frontal cortex

Authors: *C. S. SULLIVAN[1], X. ZHANG[1], M. KRATZ[2], P. MANIS[2], P. MANESS[2]
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Abstract: Establishment of a proper balance of excitatory and inhibitory (E/I) connectivity is achieved during development of cortical networks by mechanisms that are not clearly defined. Neural cell adhesion molecule NCAM and receptor tyrosine kinase EphA3 regulate perisomatic synapse density of inhibitory GABAergic interneurons onto pyramidal cells in the mouse frontal cortex through ephrin-A5-induced axonal growth cone collapse. Here we show that NCAM binds EphA3 through an interface between the extracellular NCAM immunoglobulin-2 (Ig2) domain and EphA3 cysteine-rich domain (CRD). The binding interface was further refined through molecular modeling and mutagenesis, and it was shown to be comprised of complementary charged residues in the NCAM Ig2 domain (Arg156, Lys162) and EphA3 CRD (Glu248, Glu264). Ephrin-A5 co-clustering induced activation of surface-bound EphA3 and

NCAM in GABAergic cortical interneurons in culture. NCAM enhanced ephrin-A5-induced EphA3 autophosphorylation and activation of RhoA GTPase, indicating a potentiating role for NCAM in EphA3 signaling by promoting receptor clustering.
To determine whether NCAM acts presynaptically, a novel NCAM conditional knockout mouse was generated (Parvalbumin-Cre; $NCAM^{F/F}$; Ai9 Lox-Stop-Lox tdTomato) to selectively delete NCAM from inhibitory basket and chandelier interneurons. Presynaptic deletion of NCAM led to increased numbers of perisomatic synapses of GABAergic interneurons onto cortical pyramidal cell soma. Using two-photon live-imaging of perisomatic synapse remodeling in acute brain slices, the rates of formation and elimination of perisomatic synapses were assessed in control and NCAM conditional null mice. Parvalbumin-Cre;$NCAM^{F/F}$;Ai9 mice were found to have a decreased rate of synapse elimination compared to control $NCAM^{F/+}$ mice. This phenotype is currently being correlated with behavioral studies and electrophysiology. To further assess the functional consequences of NCAM deletion on the organization of inhibitory cirtcuits in the frontal cortex, laser scanning photostimulation in brain slices of vesicular GABA transporter (VGAT)-channelrhodopsin2 (ChR2)- EYFP transgenic mice crossed to WT or $NCAM^{-/-}$ mice was performed. Results indicated that NCAM deletion increased the strength of close-in inhibitory connections to pyramidal cells of the frontal cortex, consistent with increased numbers of perisomatic synapses. The increase of inhibitory tone onto pyramidal cells likely alters E/I balance and may contribute to circuit dysfunction in neurodevelopmental diseases such as schizophrenia and bipolar disorder.

Disclosures: C.S. Sullivan: None. **X. Zhang:** None. **M. Kratz:** None. **P. Manis:** None. **P. Maness:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.08. Synaptic Plasticity

Support: KAKENHI PROJECT 17K16424

Title: Cell-cell communication may underlie radiation-induced synaptic dysfunction of mature neurons

Authors: *A. PUSPITASARI[1], N. KOGANEZAWA[3], T. SHIRAO[3], K. D. HELD[1,4], T. NAKANO[2]
[1]Gunma Univ. Initiative for Advanced Res. (GIAR) Intl. Open Labo, [2]Radiation Oncology, Gunma Univ. Grad. Sch. of Med., Maebashi, Japan; [3]Gunma Univ. Grad Sch. Med., Maebashi, Gunma, Japan; [4]Radiation Oncology, Massachusetts Gen. Hospital/Harvard Med. Sch., Boston, MA

Abstract: Radiation-induced synaptic dysfunction is of considerable interest with regards to the consequences of irradiation. In the brain, neurons are surrounded by glial cells. Neurons and astrocytes have a unique way to communicate with each other, and the healthy functional mature neurons and astrocytes must be in balance to have appropriate synaptic function. Radiation could alter this balance and affect synaptic function. Previously, we showed that a single dose of 10 Gy of X-irradiation could cause synaptic dysfunction 8 h after irradiation *in vivo*. In this study, we analyze the mechanisms of radiation-induced synaptic dysfunction which may underlie cell-cell communication such as between astrocytes and mature neurons. We investigate the synaptic function 8 h after irradiation *in vitro* using 21st days in vitro (DIV) primary hippocampal cultured neurons. We performed the irradiation in three conditions. The first condition is a single 10 Gy of X irradiation given to the astrocytes and mature neurons.The second condition is irradiating astrocytes alone, then co-culturing the irradiated astrocytes with the non-irradiated mature neurons, and the third condition is irradiating neurons alone, then co-culturing the irradiated neurons with the non-irradiated astrocytes. Cultures were then incubated for 8 h for all conditions, after which the neurons were fixed for analyzing the synaptic function. We examine the synaptic proteins using synapsin I as a presynaptic marker and drebrin as a postsynaptic marker. Radiation given to both neurons and astrocytes has effects on the resulting in a decrease of both synaptic proteins synapsin I and drebrin. Interestingly, radiation to the astrocytes and neurons alone also causes reduction of both synapsin I and drebrin of mature neurons. The decrease of drebrin in irradiated neurons alone was found to be more remarkable. This suggests that the cell to cell communication thought to be important for the radiation-induced synaptic dysfunction.

Disclosures: A. Puspitasari: None. **N. Koganezawa:** None. **T. Shirao:** None. **K.D. Held:** None. **T. Nakano:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.08. Synaptic Plasticity

Support: BBSRC

AstraZeneca Plc

Title: Exploring the molecular mechanisms underlying rapid estrogenic modulation of neuronal connectivity

Authors: *P. RAVAL[1], J. MUKHERJEE[2], K. J. SELLERS[1], S. J. MOSS[2], N. J. BRANDON[2,3], D. P. SRIVASTAVA[1]

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Abstract: There is increasing evidence that the regulation of structure and function of neuronal circuits is an essential component of normal cognitive function and behaviour. Several studies have demonstrated concurrent changes in connectivity between neurons during and following the acquisition of learned behaviours. Estrogens, particularly its biologically active form 17β-estradiol (E2), have repeatedly been illustrated to have long-lasting influences over cognitive function and behaviour, which is believed to be, in part, driven by estrogenic regulation of neuronal plasticity. Specifically, estrogens have been shown to rapidly regulate dendritic spine dynamics and shape synapse structure and function through non-genomic actions. These rapid effects can result in the initiation of signalling pathways leading to several cellular events, many of which are independent of gene transcription such as: dendritic spine turnover/remodelling; protein/receptor trafficking; and local protein translation. However, the molecular and cellular mechanisms that underlie this rapid regulation of synaptic plasticity, and enhanced cognition, have yet to be fully elucidated.

As the remodelling of neuronal connectivity is believed to be an essential component of cognitive function, we have focused on understanding the intracellular signalling pathways that are initiated by acute estrogenic treatment. Specifically, to understand how these pathways drive target protein and receptor trafficking/expression and local protein translation in response to E2 in both primary neurons and acute slices. We have previously found that there is a transient increase in dendritic spine turnover in response to acute E2 treatment, which is dependent on the P13K/Akt and ERK1/2 pathways, but independent of the mTOR pathway. What is more, by employing a combination of super-resolution imaging and biochemical assays such as Surface Sensing of Translation (SUnSET) we have found that acute E2 treatment leads to an increase in protein translation interestingly, mirroring an increase in key synaptic proteins within the cortex and hippocampus in both males and females. These data provide an insight into the signalling pathways and cellular events that potentially contribute to the effects of estrogens on dendritic spine plasticity. Thus, by further elucidating the molecular underpinnings of rapid estrogenic-modulation of hippocampal and cortical connectivity, we hope to add to the growing understanding of how estrogens influence long-lasting changes in neural circuitry and cognitive function.

Disclosures: P. Raval: None. **J. Mukherjee:** None. **K.J. Sellers:** None. **S.J. Moss:** None. **N.J. Brandon:** None. **D.P. Srivastava:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

Location: Halls A-C

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Program#/Poster#: 663.03/J6

Topic: B.08. Synaptic Plasticity

Support: JBP Foundation

The Parkinson Disease Foundation

Title: Cholinergic interneurons enhance thalamostriatal excitation of indirect pathway spiny projection neurons in a Parkinson's disease model

Authors: *A. TANIMURA[1], Y. DU[2], J. KONDAPALLI[2], D. SURMEIER[3]
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Abstract: Both the centrolateral (CL) and parafascicular (PF) nuclei of the thalamus innervate the striatum and are implicated in the control of movement and in the network pathophysiology in Parkinson's disease (PD). However, these projection systems differ both in the information they convey and in their striatal connectivity, making a rigorous dissection of how each system changes in PD models important. To this end, a BAC transgenic mouse expressing Cre recombinase selectively in the CL was used with viral delivery of Cre-off expression constructs to optogenetically interrogate the PF projection to the striatum in *ex vivo* brain slices. Following 6-hydroxydopamine lesioning of medial forebrain bundle, PF-evoked, glutamatergic responses in indirect pathway SPNs (iSPNs) were enhanced, but those of direct pathway SPNs (dSPNs) were unchanged. In parallel, PF-evoked responses in cholinergic interneurons (ChIs) were increased in this PD model. The PF-evoked responses in iSPNs were normalized by antagonism of nicotinic acetylcholine receptors (nAChRs) or by chemogenetic silencing of ChIs. Consistent with a presynaptic locus for nAChRs mediating the enhancement, the release probability of glutamate at iSPN-PF synapses was increased in the PD model and normalized by nAChRs antagonism. To determine the behavioral consequences of this feed-forward circuit, ChIs were chemogenetically silenced. This manipulations significantly improved locomotor activity and rotarod performance in the PD model, suggesting that enhanced feed-forward, presynaptic control of PF-iSPN synapses by ChIs substantively contributes to the hypokinetic symptoms of PD.

Disclosures: A. Tanimura: None. **Y. Du:** None. **J. Kondapalli:** None. **D. Surmeier:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.07. Synaptic Transmission

Support: Whitehall Foundation

NSF 1557474

Title: Calcium-dependent mechanisms underlying long-term depression of electrical synapses in the thalamic reticular nucleus

Authors: *J. S. HAAS[1], S. FITTRO[1], E. L. HECKMAN[2], J. SEVETSON[3]
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Abstract: Long-term depression (LTD) of connexin36-based electrical synapses in the rat thalamic reticular nucleus (TRN) has been demonstrated following paired burst-spiking activity and following activation of metabotropic glutamate receptors by tetanic stimulation of corticothalamic afferents, but the interactions between and downstream mechanisms of these two paradigms for LTD induction remain unclear. Using dual whole-cell recordings in brain slices containing TRN, we demonstrate that these two stimuli induce LTD by separable pathways. We show that LTD following application of the mGluR agonist ACPD occludes LTD from paired bursting in pairs of coupled TRN neurons, and LTD following paired bursting occludes ACPD-dependent LTD. We further show that burst-induced LTD depends on calcium influx via T-type channels, that calcium influx into the intracellular environment recruits calcium release from internal stores, and that the calcium-activated neuronal phosphatase calcineurin is required for activity-dependent LTD. In contrast, ACPD-induced LTD can be induced independently of those sources of calcium. Together, these results provide support for a mechanistic model whereby paired activity-induced depression is mediated by calcium entry and dynamics, while afferent activity-induced depression is not. We hypothesize that the two induction mechanisms converge at a shared downstream pathway. We discuss the implications for these two different activity inductors of LTD on thalamocortical processing.

Disclosures: **J.S. Haas:** None. **S. Fittro:** None. **E.L. Heckman:** None. **J. Sevetson:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Program#/Poster#: 663.05/J8

Topic: B.08. Synaptic Plasticity

Title: Regulation of synaptic plasticity by the dark/light cycle

Authors: *K.-W. HE[1], A. KIRKWOOD[2]
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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 in the waking states are further consolidated and enhanced during the sleep stages. Most likely these synaptic changes require activity dependent forms of plasticity: long-term potentiation (LTP) and depression (LTD). Indeed, manipulations that disrupt the induction of LTP and LTD also disrupt sleep consolidation of learning. 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) of the 12 h LIGHT cycle (mostly sleep). We found that magnitude of LTP and LTD changes in opposite ways and the end of each cycle, and in a manner consistent with the BCM model of metaplasticity.

Disclosures: K. He: None. **A. Kirkwood:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

Location: Halls A-C

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Topic: B.08. Synaptic Plasticity

Support: Swedish research council grant #3050

Swedish research council grant #2862

Title: Sonic hedgehog (Shh) control the balance between long-term potentiation and long-term depression in hippocampal neurons

Authors: *S. C. SUNDBERG, G. M. SANCHEZ, F. ANDERSSON, M. ALENIUS, B. GRANSETH
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Abstract: The morphogen Sonic hedgehog (Shh) has a well-defined role in organism development. In recent years a more regulatory role of Shh-signaling in adult organisms has been realized. Shh stimulate proliferation and differentiation of neural progenitor cells in adult hippocampus. High frequency stimulation, such as during an epileptic seizure, release Shh. It can be speculated that Shh acts to balance network activity. However, the specific role of Shh-signaling in adult brain is poorly understood. We demonstrate that blocking Shh-signaling induces dramatic changes in synaptic strength in rat hippocampal cultures. We investigated the role of Shh using patch clamp electrophysiology and confocal microscopy. Shh bind the negatively regulating receptor Patched (Ptc) resulting in an activation of the signal transducer

Smoothened (Smo). Blocking Smo during 2-3 days using the specific antagonist Vismodegib generates a massive amplitude increase in miniature excitatory post-synaptic currents (mEPSCs) compared to controls. Vismodegib block of Smo only generated increased mEPSC amplitudes in mature neurons, not in neurons during network establishment. Shh signals simultaneously via a canonical and a non-canonical signaling pathway. Interestingly, blocking the canonical pathway using GANT61 we saw an increase in mEPSC frequency but no effect on amplitude. Suggesting differing effects of the canonical and the non-canonical Shh-signaling pathway on network activity. Mechanistically we show that Vismodegib block of Smo induce an up-regulation of surface AMPA-receptors, specifically GluA1 and GluA2 subunits but not GluA3. The effect of Vismodegib on hippocampal neurons is dependent on activation of the NMDA- receptor, linking Shh to NMDA-receptor signaling. The NMDA-receptor antagonist APV blocked the effect from Vismodegib while the NMDA-receptor pore blocker MK801 reversed the effect (reduced mEPSC amplitude). Taken together, our findings show a specific role of Shh-signaling in mature networks and suggest that Shh can act to control the balance between long-term potentiation and long- term depression.

Disclosures: S.C. Sundberg: None. **G.M. Sanchez:** None. **F. Andersson:** None. **M. Alenius:** None. **B. Granseth:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.08. Synaptic Plasticity

Support: NWO VIDI 864.11.014

Title: Synaptic plasticity through activation of GluA3-containing AMPA-receptors

Authors: *E. ALBERS, M. C. RENNER, N. GUTIERREZ-CASTELLANOS, N. R. REINDERS, A. N. VAN HUIJSTEE, H. W. KESSELS
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Abstract: Excitatory synaptic transmission is mediated by AMPA-type glutamate receptors (AMPARs). In CA1 pyramidal neurons of the hippocampus two types of AMPARs predominate: those that contain subunits GluA1 and GluA2, and those that contain GluA2 and GluA3. Whereas subunits GluA1 and GluA2 have been extensively studied, the contribution of GluA3 to synapse physiology has remained unclear. Here we show that GluA3-containing AMPARs are in a low-conductance state under basal conditions, and although present at synapses they contribute little to synaptic currents. When intracellular cyclic AMP (cAMP) levels rise, GluA3 channels

shift to a high-conductance state, leading to synaptic potentiation. This cAMP-driven synaptic potentiation is mediated by the small GTPase Ras. Together, these experiments reveal a novel type of plasticity at CA1 hippocampal synapses that is expressed by the activation of AMPAR subunit GluA3.

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Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.08. Synaptic Plasticity

Support: the National Basic Research Program of China

Natural Science Foundation of China

Title: Epigenetic reprogramming during late memory reconsolidation is critical for the incubation of cocaine craving

Authors: *K. YUAN[1], Y. HAN[2], C. CHEN[3], L. LU[4]
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Abstract: Introduction: One of the challenges of addiction treatment is the incubation of drug craving, which contributes to relapse to drug use after prolonged withdrawal. The nature of drug craving is a kind of pathological memory based on modification of synaptic plasticity. Previous studies revealed a late protein synthesis-dependent phase, termed as late consolidation, for the maintenance and persistence of long-term memory traces. However, the relationship between memory late consolidation and drug incubation and the underlying mechanisms are still unknown. **Methods:** Here, using western blot, we detected the time course of changes in c-fos and DNMT3a expression following cocaine self-administration in several brain regions, including prelimbic cortex (PrL), infralimbic cortex (IL), basolateral amygdala (BLA) and central amygdala (CeA). Next, protein synthesis inhibitor anisomycin or DNA methyltransferase inhibitor RG-108 was microinjected into the PrL at different time point after last self-administration training to explore the time window of the involvement of PrL in drug memory late consolidation and its role in cocaine incubation. **Results:** We found both an early wave (0.5 h) and a late wave (18 h) of c-fos and DNMT3a expression in the PrL after cocaine self-administration training. Only an early phase of c-fos expression increased in the BLA, and there

were no significant changes in c-fos expression in the CeA. Inhibition of protein synthesis or DNA methylation 0.5 h after the last cocaine self-administration training section decreased active nosepokes during extinction test after early or prolonged withdrawal. Inhibition of protein synthesis or DNA methylation 18 h after the last cocaine self-administration training section decreased active nosepokes during extinction test after prolonged withdrawal but not early withdrawal, indicating that a delayed protein synthesis- and DNA methylation-dependent phase is required for the incubation of cocaine craving. **Conclusion:** Our results indicate that protein synthesis at definite post-training time points in the PrL is involved in cocaine incubation, and epigenetic modulation during late memory consolidation plays a critical role in this process.
Keywords: Cocaine incubation; Late consolidation; mPFC; DNA methylation

Disclosures: **K. Yuan:** None. **Y. Han:** None. **C. Chen:** None. **L. Lu:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant RO1DA040965

P30GM103398-05

Title: Cocaine conditioned place preference alters the firing properties of perineuronal net surrounded neurons in the prelimbic prefrontal cortex

Authors: *E. T. JORGENSEN[1], C. M. CASSIDY[1], B. A. SORG[2], T. E. BROWN[1]
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Abstract: Repeated drug use creates persistent drug-related memories, which contribute to chronic relapse in drug addicts. Our laboratory is interested in studying how the extracellular matrix and associated proteins contribute to the development and persistence of drug memories. Perineuronal nets (PNNs) are specialized extracellular matrix structures that primarily surround the soma and proximal neurites of inhibitory parvalbumin-containing interneurons. PNNs provide protection from oxidative stress, help regulate the ionic microenvironment, and play a significant role in synaptic stabilization. Previous work by our collaborator, Dr. Sorg, has shown that degradation of PNNs within the medial prefrontal cortex disrupts cocaine-induced reinstatement. In addition, work by us and others have shown that PNNs influence the firing properties of cells. This work looks to expand upon our previous findings and systematically define the dynamic changes in intrinsic excitability and synaptic transmission from neurons with

and without PNNs within the prelimbic PFC (PL-PFC) following acute and repeated cocaine exposure. To characterize the electrophysiological properties of cells within the PL-PFC, brain slices from male Sprague Dawley rats were prepared following cocaine conditioned place preference (cocaine-CPP) and whole-cell recordings were performed. PNN positive cells were identified by Wisteria floribunda agglutinin (WFA)-induced fluorescence. Cocaine-CPP decreased the firing patterns of WFA(+) and WFA(-) interneurons relative to naive controls. However, for acute exposure to cocaine we only observed an attenuation in spike number in the WFA- neurons. This suggests that WFA(+) neurons may only be sensitive to intrinsic adaptations following repeated exposure to cocaine. Through this work, we hope to identify the functional consequences of cocaine-induced PNN changes, which may lead to novel therapeutics for the treatment of drug addiction.

Disclosures: E.T. Jorgensen: None. **C.M. Cassidy:** None. **B.A. Sorg:** None. **T.E. Brown:** None.

Poster

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Topic: B.08. Synaptic Plasticity

Support: JSPS Grant 16K08070

Title: Age-dependent alteration of oxidative stress and expression level of glutamate receptors in senescence-accelerated mouse prone 8

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Abstract: Senescence-accelerated mouse (SAM) developed through selective inbreeding of the AKR/J strain shows short lifespan and rapid advancement of senescence. Many behavioral tests revealed that SAM prone 8 (SAMP8) exhibits age-related deficits on learning and memory. However, the basic mechanism of loss of cognitive function remains still unclear. Progression of aging is thought to be induced by systemic oxidative stress. Recently, new approaches to evaluate reactive oxygen species using an indicator termed Diacron-Reactive Oxygen Metabolites (d-ROM) and reduction capacity using Biological Antioxidant Potential (BAP) measurement have been developed. Besides, aging impairs the cognitive performance in association with degradation of the synaptic plasticity in which N-methyl-d-aspartate receptor (NMDAR) plays a crucial role. To test if the alteration of oxidative stress and/or expression of glutamate receptors underlies the decline of cognitive function with aging, we quantitatively investigated the d-ROM and BAP values and expression levels of glutamate receptors with age

using SAMP8 in this study. After we confirmed if SAMP8 has a short life-span in our experimental environment compared with SAM resistant 1 (SAMR1), which is the control strain of SAMP8, we measured the d-ROMs and BAPs from the blood serum of SAMR1 and SAMP8. The d-ROM level of 1-year-old SAMP8 was significantly higher than not only that of age-matched SAMR1 but also that of 6-month-old SAMP8, although 2-year-old SAMR1 showed higher d-ROM level compared to 6-month and 1-year-old SAMR1. BAP level was the highest in 6-month-old SAMP8, whereas SAMR1 presented the sustained BAP values for its entire life. These results indicate that the d-ROM level of SAMP8 elevated earlier than SAMR1 and that antioxidant capacity decreases with age in SAMP8 but not in SAMR1. Next, we studied the protein expression of NMDAR subunits, that is, GluN1, GluN2A and GluN2B. All NMDAR subunits decreased with age in both SAMR1 and SAMP8 although no significant differences were observed between these strains. The inconsistency of oxidative stress level and NMDAR expression remains to be solved currently in progress.

Disclosures: S. Taniguchi: None. **M. Hanafusa:** None. **H. Tsubone:** None. **D. Yamanaka:** None. **K. Ito:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 663.11/K2

Topic: B.08. Synaptic Plasticity

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CIBERNED (CB06/05/0042)

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Generalitat de Catalunya (SGR2009-1231)

Title: Analysis of synaptic-related microRNAs expression in Alzheimer's disease

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Abstract: MicroRNAs (miRNAs) are small non-coding RNA molecules that fine-tune gene expression at post-transcriptional level. Recent studies have shown that deregulation of specific miRNAs could be involved in the development and progression of Alzheimer's disease (AD).

However, few studies have explored the relationship between miRNAs deregulation in AD and synaptic plasticity despite the involvement of some miRNAs in synaptic plasticity. Moreover, a comprehensive analysis of the miRNome during AD progression is lacking. In this study, we performed a microarray analysis (Affymetrix® miRNA 4.1) in the entorhinal cortex, hippocampus, prefrontal cortex and cerebellum of AD patients at different Braak stages. We found that 47 miRNAs were deregulated in the entorhinal cortex (17 down-regulated and 30 up-regulated) and 23 in the hippocampus (17 down-regulated and 6 up-regulated) at Braak stage I/II compared to age-matched non-demented controls. miRNAs targeting synaptic-related mRNAs were identified using the miRWalk database and validated by RTqPCR. qPCR analysis confirms a reduction of several miRNAs including miR-92a-3p (log2 relative expression = -0,7 ± 0,33), miR-181c-5p (log2 relative expression = -0,46 ± 0,33) and miR-210-3p (log2 relative expression = -1,16 ± 0,42) levels during early stages of AD (Braak I/II) in the entorhinal cortex, but not in the hippocampus. Our results show altered levels of specific miRNAs related to synaptic plasticity processes, which may play important roles during early AD pathology.

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Poster

663. Synaptic and Neuronal Plasticity Mechanisms

Location: Halls A-C

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Title: Astrocytic activation generates de-novo neuronal potentiation and memory enhancement

Authors: ***A. KOL**, A. ADAMSKY, T. KREISEL, T. MELCER, R. REFAELI, L. REGEV, M. LONDON, I. GOSHEN
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Abstract: Astrocytes are capable of sensing synaptic activity and responding to it with complex internal calcium signaling. Evidence obtained in the last two decades suggests that astrocytes not only respond to neuronal activity but may also directly affect synaptic function and create dynamic bidirectional communication with neurons. In this work we examined whether synaptic plasticity and behavior can be modulated purely by activating astrocytes. We specifically modulated astrocytic calcium activity by expressing the Gq-coupled designer receptor hM3Dq in hippocampal CA1 astrocytes to test the effect of astrocytic calcium signaling on synaptic transmission.We found that astrocytic Gq pathway activation increased both frequency and amplitude of neuronal spontaneous release events. Furthermore, we discovered that astrocytic activation is not only necessary for synaptic plasticity, but sufficient to induce *de-novo* potentiation of CA3 to CA1 synapses. These plastic changes manifested in behaving mice as marked memory enhancement in mice with already intact memory. A similar recall enhancement was not achieved by randomly increasing neuronal activity directly, which in fact dramatically impaired memory. Our findings show for the first time that astrocytic manipulation can induce de-novo synaptic potentiation which result in enhanced memory acquisition.

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Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.08. Synaptic Plasticity

Support: JSPS KAKENHI Grant Numbers 24500598

Title: Activation of neuroplasticity pathways in the rat spinal cord through treadmill exercise

Authors: *Y. OKA[1], ***Y. OKA**[1], Y. SHIROSE[2], N. KUWABARA[1], K. NAKAMOTO[3], T. KOKUBUN[4], K. MURATA[1], N. KANEMURA[4]
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Abstract: Exercise is recommended to prevent disease and improve physical function. Previous studies have reported that treadmill running greatly affects the expression of neurotrophic factor in rats. However, intracellular signaling involving the phosphatidylinositol 3-kinase (PI3K)/Akt pathway needs to be assessed to confirm activation of the cell. Therefore, we assessed rats of different ages, which performed running exercise, to determine the influence of age and exercise on the PI3K/Akt pathway. Thirty-eight rats were randomly assigned to two groups: treadmill-

exercised (ages: 10 weeks, 6 and 12 months [n=5 for each], and 24 months [n=3]) and nonexercised (ages: 10 weeks, 6, 12, and 24 months [n=5 for each]). The exercise consisted of 3.6 m/min (10 min) → 5.8 m/min (50 min) for 4 weeks (5 days a week). After the exercise, we collected their lumbar spinal cords. Primary antibodies against PI3K, Akt, and cAMP response element binding (CREB) were used for the immunohistochemical staining. Cross-sectional staining intensity > 50 was considered positive. The cells were counted (cell counts) with image analysis software and classified by cross-sectional area (100-499 or 500-799 μm^2). The groups were compared with a two-way factorial analysis of variance and Bonferroni correction for multiple comparisons. The numbers of PI3K-positive cells were significantly increased in the 100-499-μm^2 (glial cells) and 500-799-μm^2 (motor neurons) areas in the 12-month-old exercised group compared with the nonexercised group ($p < 0.05$). In the 12-month-old exercised group, the levels of expression of PI3K in the glial cells and motor neurons were significantly increased compared with the 24-month-old exercised rats ($p < 0.01$). No significant differences in the levels of Akt or CREB were found among the groups, but the levels of expression tended to be increased in the exercised groups compared to the nonexercised groups. The PI3K results showed that, in the 12-month-old rats, exercise increased the expression of neurotrophic factor, which is produced by muscle and nerve cells, and activated part of the activation pathway in motor neurons. These results suggested that running exercise only slightly activated neurons at 24 months of age because of age-related deterioration of the metabolic function of cells and the shedding of motor neurons. The trend for the increased expression of Akt and CREB may influence the activation of neurons. A previous study reported that running at 10 m/min increased the expression of trophic factors at 6 months of age. However, the result of this study, wherein the rats ran at about half the speed, indicated that cells were not activated at 10 weeks or 6 months of age.

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Poster

663. Synaptic and Neuronal Plasticity Mechanisms

Location: Halls A-C

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Topic: B.08. Synaptic Plasticity

Support: Italian Ministry of University and Research (SIR 2014 - RBSI14ZV59)

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Title: FoxO3a/Zdhhc3/AMPA receptor GluR1 cascade at the crossroad between insulin resistance and impairment of synaptic plasticity and memory

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Abstract: High-fat diet (HFD) and metabolic diseases cause detrimental effects on hippocampal synaptic plasticity, learning and memory through molecular mechanisms still poorly understood. Mice fed a HFD for 6 weeks showed reduced long-term potentiation (LTP) at CA3-CA1 synapses (standard diet [SD] = 186.2 ± 19.9%, HFD = 123.6 ± 8.1%; n=9 for each group; $p<0.05$) and memory deficits evaluated by novel object recognition test (preference index: SD = 67.9 ± 1.8%, HFD = 59.2 ± 1.6%; n=10 for each group; $p<0.001$) and Morris water maze task (time spent in the target quadrant during the probe test: SD = 34.6 ± 1.3 s, HFD= 21.4 ± 1.3 s; n=8 for each group; $p<0.001$). HFD mice also exhibited increased palmitic acid deposition in the hippocampus and brain insulin resistance leading to FoxO3a-mediated overexpression of the palmitoyl-transferase Zdhhc3. The excess of palmitic acid along with higher Zdhhc3 levels induced hyper-palmitoylation of AMPA glutamate receptor subunit GluR1 (+30 ± 1%; n=5; $p<0.05$) and reduced its phosphorylation at serine 845 (-35 ± 1%; n=4; $p<0.05$). To deeply investigate the molecular mechanism underlying the diet-dependent change of GluR1 palmitoylation we set up an *in vitro* model resembling the *in vivo* metabolic stress. Mouse hippocampal neurons treated for 24h with 20 nM insulin and 200 µM palmitic acid (IPA) showed: i) increased GluR1 palmitoylation/S845 phosphorylation ratio; ii) reduced GluR1 trafficking to the plasma membrane and lower binding with PSD-95 (-70 ± 2% of controls; n=4; $p<0.01$); iii) loss of GluR1 activation upon a chemical LTP protocol. Accordingly, AMPAR current amplitudes and, more importantly, their potentiation underlying synaptic plasticity, were inhibited upon IPA treatment. Strikingly, both hippocampus-specific silencing of ZDHHC3 and intranasal injection of a palmitoyl-transferase inhibitor counteracted GluR1 hyper-palmitoylation and restored synaptic plasticity and memory in HFD mice. Our data reveal a key role of FoxO3a/Zdhhc3/GluR1 axis in the HFD-dependent impairment of cognitive function and identify a novel mechanism underlying the crosstalk between metabolic and cognitive disorders.

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Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.08. Synaptic Plasticity

Support: The Scientific and Technological Research Council of Turkey (TUBITAK) 1001 grant 214S236

Title: Effects of short-term of caloric restriction and rapamycin treatments on cellular and synaptic components in young and old zebrafish (Danio rerio)

Authors: D. CELEBI-BIRAND[1,2,3], G. F. SENGUL[1,2,3], N. I. ARDIC[1,2,3], H. KAFALIGONUL[4,2], *M. M. ADAMS[5,2,3]
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Abstract: Understanding the cellular and synaptic mechanisms underlying brain aging provides insight into potential therapeutic targets for interventions. The only nongenetic intervention that reliably increases life- and healthspan is caloric restriction (CR), a dietary regimen based on lowering daily caloric intake. Life-long calorically-restricted animals have delayed age-related physiological changes and prevention of some cellular and synaptic alterations in the brain. CR and its potential mimetic, rapamycin, have been found to exert their effects through the mammalian target of rapamycin complex in the nutrient signaling pathway. Currently there is a paucity of information on the short-term effects of CR and its potential mimetics, as well as similarities in their cellular mechanisms. In the present study, we investigated whether different short-term durations of CR and rapamycin treatment had beneficial effects on key synaptic proteins known to deteriorate with age, and whether rapamycin similarly mimics CR's beneficial effects. Wild type AB strain young (9-11 months) and old (27-33 months) zebrafish, maintained in standard conditions, were used to determine whether the brain responds to CR and rapamycin. To date only a few studies have performed true CR regimens on zebrafish, which has become a popular model to study brain aging. Six groups were included for a total of 115 animals. There were *ad libitum* (AL)-fed fish receiving no drug treatment, AL-fed animals with rapamycin treatment, and animals calorically-restricted with an every-other-day feeding approach. Four, six and eight weeks of CR and rapamycin treatment were examined to identify differential effects on body weight and length, key synaptic protein levels, and cortisol levels. Aquaria parameters such as water pH, nitrate levels, and temperature were monitored closely to minimize stress, and also maintain optimal housing conditions. Following euthanization, body weight and length were measured, brains were dissected for Western blot analysis, and bodies were analyzed for

measurements of cortisol levels. As expected our results demonstrated significant changes in body weight (30% reduction in CR groups, increases in AL and Rapamycin groups, 30% and 35% respectively). These data suggest that zebrafish respond to CR and rapamycin treatment in an expected manner, and are an appropriate model to investigate the potential effects of CR and rapamycin on brain aging. Moreover, our findings indicated that the longer treatment (8 weeks) was more effective than shorter ones (4 and 6 weeks). Studies are continuing to determine specific treatment effects on synaptic protein and body cortisol levels.

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Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.08. Synaptic Plasticity

Support: AHFMR/AIHS Polaris

Title: Experience dependent spatio-temporal changes in the early and late evoked patterns of cortical activity in anesthetized mice using wide-field voltage-sensitive dye imaging

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Abstract: The evoked response in the primary sensory areas of the brain is divided into two components, an early response and a late response. The early component usually lasts for less than 100 ms after stimulus onset, is associated with direct thalamo-cortical connections and encodes the stimulus features. Conversely, the late response starts around 200 ms after stimulus onset, lasts a couple of hundred ms and is associated with sensory perception.
One characteristic of perception is that it is not fixed but it can be modified by experience. Therefore, one can ask whether the perceptual signal observed during the late evoked response could be modified by experience and if so, in what way? In addition, the cortical dynamics of the evoked response is not limited to the corresponding sensory area but propagates extensively across the cortical mantle. Moreover, perception involves complex processes in multiple and distributed cortical areas. Therefore, it is important to study the spatiotemporal dynamics of the late sensory evoked response at the mesoscale level.
We use wide-field Voltage-sensitive dye imaging over most of the right hemisphere to compare sensory evoked activity before and after tetanic stimulation in urethane anesthetized mice injected with amphetamine. We observed that the spatiotemporal evoked pattern changes

significantly during the late response after tetanic stimulation. In particular, the amplitude of the late evoked response increases after tetanic stimulation. To evaluate whether the observed changes are stimulation dependent, we give tetanic auditory stimulation first and compare the evoked responses of the auditory (AC) and somatosensory cortices (SS) before and after the tetanic stimulation. Subsequently, we give tetanic hindlimb stimulation and compared again the auditory and somatosensory evoked responses. When we give tetanic auditory stimulation we observe an increase of the late evoked response in AC but not in the SS. Subsequently, when we give tetanic hindlimb stimulation we observe an increase in the late response in SS and a decrease of the late response in AC. Moreover, we show that after tetanic stimulation, the spatiotemporal evoked pattern during the late response resembles more closely the pattern of the early response. These experience dependent spatiotemporal changes observed during the late evoked response could be a top-down cortical mechanism to enhance early sensory processing. Our results provide evidence of experience dependent spatiotemporal changes in the late evoked response that can help to clarify the relationship between sensory perception and cortical plasticity at the mesoscale level.

Disclosures: E.J. Bermudez Contreras: None. **A. Luczak:** None. **M. Mohajerani:** None. **B. McNaughton:** None.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.07. Synaptic Transmission

Support: NIH R01 NS086100

Title: Deep brain stimulation induced synaptic depletion is a robust phenomenon independent of synapse type

Authors: A. FAROKHNIAEE[1], R. W. ANDERSON[2], *C. C. MCINTYRE[3]
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Abstract: Deep brain stimulation (DBS) is a successful clinical therapy for a wide range of neurological disorders; however, the physiological mechanisms of DBS remain unresolved. Computational models of DBS commonly suggest robust generation of DBS-induced action potentials (APs) in neural pathways that course by the electrode and that those APs propagate to their axon terminals. From a network activity perspective, the fundamental effect of AP invasion into a synaptic terminal is transmitter release. However, little attention is typically paid to quantifying the actual synaptic effect of the DBS-activated pathways on their post-synaptic

targets. We propose that one hypothesis that can help explain the mechanisms of DBS is the exhaustion of synaptic transmitter release in directly stimulated pathways. Synapses typically have a readily releasable pool of neurotransmitters packaged in vesicles and machinery to replenish that pool once they are released. However, high frequency (~130 Hz) driving of a synapse quickly exhausts the readily releasable pool and overwhelms the recycling machinery. In turn, postsynaptic currents (PSC) during DBS can be dramatically reduced, effectively eliminating the ability of the synapse to modulate the post-synaptic neuron or transmit any information. This basic phenomenon can be most easily studied at glutamatergic synapses where a wealth of experimental data is available to parameterize the model. However, multiple glutamatergic synapse types are known to exist, including Depressing (D), Facilitating (F), and Pseudo-Linear (PL). Therefore, we set out to quantify how these different synapse types would respond to DBS. We used a leaky integrate and fire (LIF) neuron model to evaluate the post-synaptic response to DBS-driven synaptic inputs. Our theoretical results suggest that the synaptic depletion is a robust effect in DBS activated glutamatergic pathways, independent of the synapse type. In turn, DBS effectively creates a "synaptic lesion" in directly stimulated pathways and this mechanism is especially relevant to DBS of the hyperdirect pathway for the treatment of Parkinson's disease.

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Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Topic: B.08. Synaptic Plasticity

Support: NSF GRFP DGE-1321846

Title: Transcranial direct current stimulation enhances SSVEP response over multiple days: A role for consolidation

Authors: *J. AU[1], S. JAEGGI[1], S.-M. MOON[1], B. GIBSON[1], R. SRINIVASAN[2]
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Abstract: Transcranial direct current stimulation (tDCS) is a form of noninvasive brain stimulation that has been increasing in popularity over the past decade, both within and without the scientific community. Among its many touted effects include cognitive enhancement, motor rehabilitation, and depression management, to name a few. Nevertheless, despite its rise in popularity, there has not been a proportionate increase in mechanistic understanding. The putative mechanism of action most widely described by researchers is a polarity-dependent shift in the resting membrane potential of target neurons lying in the path of the current, resulting in a

polarity-dependent change in cortical excitability. This mechanism is derived from *in vitro* work, and supported by *in vivo* human studies in which motor-evoked potentials (MEP) have been demonstrated to respectively increase or decrease in strength after anodal or cathodal stimulation to the motor cortex. Results from these *in vitro* and motor studies have been extrapolated to guide translational tDCS research in other cortical areas. However, few studies have actually sought to investigate basic tDCS effects on neural activity outside the motor cortex. The present study uses EEG to measure steady-state visual evoked potentials (SSVEP) as an extra-motor analogue of MEPs to investigate short- and long-term excitability effects of tDCS over the parietal cortex. In a within-subjects design, participants came in over three consecutive days and were randomly assigned to receive two sessions of active tDCS and one session of sham tDCS in a counterbalanced manner. SSVEPs were measured with EEG before and after tDCS, and a visual working memory task was also performed. Results showed that SSVEP power increased after active, but not sham tDCS, but only when measured the next day. We conclude that tDCS can promote consolidation of sensory networks in the parietal cortex, and that these consolidation effects are more robust than any immediate excitability changes brought upon by putative shifts in resting membrane potential. Furthermore, we confirm SSVEP as a tool to study basic tDCS effects over the parietal cortex, and provide a critical avenue for the field to advance its mechanistic understanding of tDCS in brain regions outside the motor cortex.

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Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Program#/Poster#: 663.19/K10

Topic: B.08. Synaptic Plasticity

Title: Electrophysiological effects of theta burst stimulation in humans: An electrocorticography (ECoG) study

Authors: J. L. HERRERO[1], A. D. MEHTA[2], C. KELLER[3], E. H. CHANG[4], *M. ARGYELAN[5]
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Abstract: Long-term potentiation (LTP) has been investigated extensively in animal studies as an important mechanism of experience-dependent plasticity in the brain, including learning and memory. The recent introduction of transcranial magnetic stimulation (TMS) has provided the

opportunity to investigate similar mechanisms in the intact human brain with protocols of repetitive TMS (rTMS) that resemble those used in experimental preparations. The therapeutic effects of rTMS are encouraging, however, little is known about the underlying neurophysiological mechanisms in the intact brain.We performed invasive recordings from epilepsy patients with electrodes implanted in the motor cortex. Intermittent theta burst stimulation, a type of excitatory rTMS which has recently shown strong effects, was applied to the motor cortex. Motor thresholds, cortico-cortical evoked potentials (CCEPs) were conducted before and after iTBS interleaved with baseline resting ECoG periods for ~ 1hour. We found that motor thresholds were reduced after ITBs, and that they gradually recovered over the course of 1 hour. Time-frequency analysis of the CCEPs revealed a strong beta burst ~200ms after stimulation which was reduced after iTBS and gradually recovered over the course of ~1 hour. Analysis of CCEPs N1 and N2 responses showed increased peak amplitude after iTBS but the effect fail to completely wash out. These effects may contribute to the understanding of the therapeutic potential of these methods in treating patients with neuropsychiatric disorders.

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Poster

663. Synaptic and Neuronal Plasticity Mechanisms

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Title: Test-retest reliability of the effects of continuous theta-burst stimulation (cTBS) in healthy adults

Authors: *A. JANNATI[1], P. J. FRIED[1], G. BLOCK[1], L. M. OBERMAN[2], A. ROTENBERG[3], A. PASCUAL-LEONE[1]

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Abstract: Objective: To evaluate the reliability of cTBS aftereffects as indices of the efficacy of the mechanisms of cortical plasticity, and to test whether cTBS reliability is modulated by brain-derived neurotrophic factor (*BDNF*) and apolipoprotein E (*APOE*) polymorphisms.
Methods: 28 healthy adults (25 males, age 36.8 ± 14.5) underwent cTBS of the left primary motor cortex (M1) at 80% active motor threshold (AMT). Cortico-motor reactivity was measured before and after cTBS by sets of 30 biphasic, single pulses of neuronavigated transcranial magnetic stimulation (TMS) applied to M1 at 120% resting motor threshold (RMT). TMS was performed with a MagPro X100 stimulator, MC-B70 Butterfly Coil, and Brainsight neuronavigation. Two identical visits (7-33 days apart; median interval = 9.5 days) were conducted per participant. Saliva samples from 22 participants were used to assess *BDNF* and *APOE* polymorphisms.
Motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous muscle. Log-transformed, baseline-corrected MEP amplitudes (LnMEPs) were calculated at 5-, 10-, or 15-minute intervals post-cTBS (*T5*-*T120*). Intraclass correlation coefficients (ICCs) were calculated to assess reliability.
Results: LnMEP measures were most reliable at T50 (ICC = 0.53), followed by T30 (ICC = 0.37). This order was reversed for *absolute* LnMEP values (|LnMEPs|) which were most reliable at T30 (ICC = 0.50), followed by T50 (ICC = 0.34). Reliability of maximum MEP depression (ICC = 0.38) and maximum absolute modulation (ICC = 0.31) were in range of other measures.
LnMEP area-under-the-curve (AUC) was the most reliable if derived from T0-T60 values (ICC = 0.40), followed by T0-T120 and T0-T50 (ICCs = 0.37 and 0.36). All |LnMEPs| AUCs over T0-T50 and beyond had ICCs >= 0.42.
LnMEPs at T20, T30, T40, T90, and T105 were significantly more reliable in 14 participants with the Val66Val *BDNF* single-nucleotide polymorphism (ICCs = 0.64, 0.50, 0.60, 0.46, and 0.52) than in 8 participants with the Val66Met variant (ICCs = -0.47, -0.42, -0.09, -0.09, and -0.01), p's < 0.016.
LnMEPs at T5, T20, T30, T40 were significantly more reliable in 12 *APOE* ε4- participants (ICCs = 0.49, 0.52, 0.81, 0.64) than in 10 *APOE* ε4+ participants (ICCs = -0.12, -0.31, -0.12, 0.07), p's < 0.024.
Conclusions: As reflected in altered MEP amplitude, cTBS aftereffects are most reliable when obtained 30 or 50 minutes after cTBS, or when the AUC is calculated over at least 50 minutes post-cTBS. The reliability of cTBS aftereffect is significantly lower in *BDNF* Val66Met and *APOE* ε4+ participants.
Acknowledgment. The study was primarily supported by the National Institutes of Health (R01 MH100186).

Disclosures: **A. Jannati:** A. Employment/Salary (full or part-time):; Postdoctoral Fellowship from Natural Sciences and Engineering Research Council of Canada (NSERC PDF 454617). **P.J. Fried:** None. **G. Block:** None. **L.M. Oberman:** None. **A. Rotenberg:** F. Consulting Fees (e.g., advisory boards); Neuromotion, NeuroRex. **A. Pascual-Leone:** F.

Consulting Fees (e.g., advisory boards); Magstim, Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Constant Therapy, and Neosync.

Poster

663. Synaptic and Neuronal Plasticity Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 663.21/K12

Topic: B.08. Synaptic Plasticity

Support: R01 MH100186

R01 HD069776

R01 NS073601

R21 MH099196

R21 NS085491

R21 HD07616

UL1 RR025758

Title: Continuous theta-burst stimulation as a neurophysiologic biomarker for children with autism spectrum disorders

Authors: *G. BLOCK[1], A. JANNATI[1], H. L. KAYE[2], L. M. OBERMAN[3], A. PASCUAL-LEONE[1], A. ROTENBERG[2]
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Abstract: Objectives: To evaluate the measures of cortical plasticity by continuous theta-burst stimulation (cTBS) as a potential physiologic biomarker for children with autism spectrum disorders (ASD). Previous studies have found TBS-induced hyperplasticity in adults with ASD (IQ > 70) compared to controls.
Methods: 10 children with non-syndromic ASD (9 males, age mean ± *SD*, 13.2 ± 2.0, IQ > 70), and 7 neurotypical children (NT; 2 males, age 10.0 ± 3.7, IQ > 70) underwent cTBS consisting of bursts of three pulses of 50 Hz stimulation at 80% individual active motor threshold, repeated at 200 ms intervals for 40 seconds (for a total of 600 pulses). Cortico-motor reactivity was assessed before and after cTBS by single pulses of transcranial magnetic stimulation (TMS) with a figure-of-eight coil to the left primary motor cortex (M1) at 120% of individual resting motor threshold. Peak-to-peak amplitudes of motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous muscle. Log-transformed, baseline-corrected, average MEP

amplitude (LnMEP) was calculated at 5-, 10-, or 15-minute intervals between 5 and 120 minutes post-cTBS (*T5–T120*). Saliva samples were collected from children with ASD to assess the effect of *BDNF* Val66Met polymorphism on cTBS-induced cortical plasticity.
Results: Although cTBS in healthy adult volunteers most commonly induces depression of the MEPs, the hand MEPs were potentiated in 50% of pediatric subjects with ASD. The extent of maximum MEP modulation in response to cTBS was greater in the ASD group than in the NT group ($p = .026$). Within the ASD group, *BDNF* Val/Met children showed greater suppression of LnMEPs than *BDNF* Val/Val children at all post-cTBS time points (T5–T120). This difference was statistically significant at T50 ($p = .028$).
Within the ASD group, age was positively correlated with larger maximum suppression of LnMEPs ($p = .02$). This relationship was not significant in the overall group ($p = .61$) or in the NT group ($p = .46$).
Conclusions: Our results support the value of exploring cortical plasticity measures by cTBS as a physiologic biomarker in children with ASD further. The contribution of *BDNF* isoform and age to cTBS-induced plasticity in the ASD group provide further insight into interindividual differences in cTBS measures of cortical plasticity. This may also indicate impaired *BDNF*-mediated cortical plasticity in children with ASD.
This work was supported by NIMH R01 1000186.

Disclosures: G. Block: None. **A. Jannati:** None. **H.L. Kaye:** None. **L.M. Oberman:** None. **A. Pascual-Leone:** F. Consulting Fees (e.g., advisory boards); Magstim, Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, and Neosync. **A. Rotenberg:** F. Consulting Fees (e.g., advisory boards); Neuromotion and NeuroRex.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.01/L1

Topic: B.11. Epilepsy

Support: NIH Grant P20GM103442

NSF Grant IIA-135466

NIH Grant R01-HL098279

Title: α_{1A}-adrenergic receptor activation decreases epileptiform activity in the murine hippocampal CA3 region

Authors: *J. P. BIGGANE[1], Z. O. DENT[1], D. M. PEREZ[2], V. A. DOZE[1]
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Abstract: Norepinephrine (NE) is a well-known modulatory neurotransmitter, signaling via the adrenergic receptors (ARs), that mediates a potent antiepileptic effect *in vivo*. Previous studies suggest that α_1-ARs may underlie part of this antiepileptic effect, possibly by effecting inhibitory GABAergic interneuron activity. The α_{1A}-AR is of particular interest because we found that α_{1A}-AR knockout mice experience frequent spontaneous seizures while α_{1B}-AR knockout mice were somewhat resistant to seizures. Importantly, we also found that α_{1A}-AR activation improves memory, mood, and synaptic plasticity; which directly opposes most other antiepileptic mechanisms. In this study, we have further elucidated the pharmacology and physiology of α_{1A}-AR activation on epileptiform activity generated using low magnesium in acute hippocampal slices. Spontaneous epileptiform activity was measured using electrophysiological field potential recordings in the *stratum pyramidale* of the CA3 hippocampus. Slices were treated with α_1-AR-selective agonists (phenylephrine, epinephrine, A61603, or cirazoline), alone or in the presence of an α_{1A}-AR-selective antagonist (5-methyl urapidil) or $GABA_A$ receptor blocker (picrotoxin). Our results suggest that α_1-AR activation leads to a significant decrease in epileptiform activity (30-50% depending on the agonist), while α_{1A}-AR blockade abolishes agonist-induced reductions in frequency, in the absence of influence from α_2-ARs and β-ARs. Furthermore, $GABA_A$ receptor blockade also eliminated the α_1-AR-mediated reduction in epileptiform activity. Overall, α_{1A}-AR activation was shown to be the predominant subtype responsible for α_1-AR-mediated antiepileptic effects, likely via modulation of inhibitory GABAergic interneuron activity.

Disclosures: **J.P. Biggane:** None. **Z.O. Dent:** None. **D.M. Perez:** None. **V.A. Doze:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.02/L2

Topic: B.11. Epilepsy

Support: National Science Foundation 1264948

Jilin 20160414006GH

Title: Interictal and ictal events are different cortical response to same global thalamic input

Authors: *H. MA[1], E. BAIRD-DANIEL[1], J.-Y. LIOU[2], M. ZHAO[1], D. LI[3], C. A. SCHEVON[2], T. H. SCHWARTZ[1]

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Abstract: Rationale: Interictal spikes (IISs) are the hallmarks of the presence of an active epileptic focus. However, the relationship between IIS and ictal events has been widely debated. While some studies indicate that IIS may trigger an interictal-to-ictal transition, it is also reported that interictal events may play a role in the control of seizures. The main reason for this debate relies on the lack of knowledge on the initiation dynamics of both IIS and ictal events. Here, we observe the initiation processes of both IIS and ictal events in a focal neocortex epilepsy model. Methods: The focal epilepsy model was created by local injection of 4-Aminopyridine (15mM, 0.5 μl) (4-AP) and the local field potential was recorded from the 4-AP injection electrode. Wide field calcium imaging was employed for wide-field recording of neuronal activity. Multielectrode arrays (10 by 10 grid, 40 μm spacing) were used to recorded local field potential and multiunit activity. In some experiments, local field potentials were recorded from both the neocortex and the thalamus. A bipolar electrode with an interelectrod distance of 150 μm was employed to deliver single or train squire wave stimulation to the ventrolbasal thalamus. Results: The 4-AP induced ictal events were focally distributed near the 4-AP injection site, the ictal focus. On the other hand, the ictal first spike and IISs propagated to the whole field of view. Both IIS and the first spike initiated from cortical areas far removed from the ictal focus and propagated back into the focus. During both the first spike and IIS, thalamic involvement reliably lead the cortical activity. These results indicate that both ictal events and the IIS were triggered by thalamocortical connections. This was further supported by the observation that TTx injection into the thalamus suspended both IIS and ictal events. We then delivered electrical stimulation to the ventrolbasal thalamus. Single or a train of square-wave stimulation was found to trigger the onset of both the first spike of ictal event and the IIS. Conclusion: We demonstrate that IIS and the first spike of ictal events have similar spatiotemporal dynamics and are both triggered by thalamocortical input. Our data indicates that IIS and ictal events may be arise as different cortical response to a global thalamic input.

Disclosures: H. Ma: None. **E. Baird-Daniel:** None. **J. Liou:** None. **M. Zhao:** None. **D. Li:** None. **C.A. Schevon:** None. **T.H. Schwartz:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.03/L3

Topic: B.11. Epilepsy

Support: University of Virginia Medical Scientist Training Program

Title: A heterogeneous thalamic network model that recapitulates oscillations modulated by GABA transporter blockade

Authors: *A. LU[1], C. K. LEE[4], B. TRUONG[2], J. R. HUGUENARD[5], M. P. BEENHAKKER[3]
[1]Med. Scientist Training Program, [3]Pharmacol., [2]Univ. of Virginia, Charlottesville, VA; [4]Dept. of Neurol. and Neurolog. Sci., Stanford Univ. Sch. of Med., Palo Alto, CA; [5]Dept Neurol & Neurolog. Sci., Stanford Univ. Sch. Med., Palo Alto, CA

Abstract: Absence seizures are thought to result from 3~5 Hz generalized thalamocortical oscillations. Understanding how such oscillations persist could lead to novel treatments for the most common form of pediatric epilepsy. Previous work has shown that electrically-induced oscillations in acute thalamic slices were prolonged upon pharmacological blockade of GABA transporters GAT1 or GAT3 individually, but were suppressed upon dual blockade of GAT1 and GAT3. We sought to understand this paradox by developing a biophysical thalamic network model that can recapitulate these findings. To this end, we first used pharmacological manipulations to isolate 4 distinct temporal profiles of inhibitory post-synaptic currents from GABAB receptors of thalamocortical (TC) relay neurons. Each profile corresponded to a particular pharmacological condition: (1) control, (2) GAT1 blockade, (3) GAT3 blockade, (4) dual blockade. Then, using dynamic clamp, we recorded voltage responses of 36 TC neurons to each of these 4 GABAB IPSC profiles. By simulating IPSC responses in a 3-compartment single neuron model and fitting them to all experimental data, we sought to determine those neural parameters that account for inter-cell variability and those parameters that account for inter-trial variability. Finally, we combined the distinct single neuron models into a heterogeneous thalamic network model to simulate intrinsic oscillations modulated by distinct GABAB IPSC profiles. In summary, we have developed a biophysically-based computational model that recapitulates most effects of GABA transporter antagonists on thalamic oscillations. These results will suggest that modulation of GABA transporters is a potential novel treatment for absence epilepsy.

Disclosures: A. Lu: None. **C.K. Lee:** None. **B. Truong:** None. **J.R. Huguenard:** None. **M.P. Beenhakker:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.04/L4

Topic: B.11. Epilepsy

Support: NIH R01NS097762

Title: Chemogenetic silencing of projections from the basolateral amygdala to the mediodorsal thalamus attenuates limbic seizures

Authors: *E. WICKER[1], P. A. FORCELLI[1,2]
[1]Pharmacol. and Physiol., [2]Interdisciplinary Program in Neurosci., Georgetown Univ., Washington, DC

Abstract: The mediodorsal thalamus (MD) has been theorized to play a key role in seizure propagation (Bertram et al., 2008), in part due to its direct connections with key ictogenic structures including the hippocampus, piriform cortex and basolateral amygdala (BLA). Indeed, upon stimulation of the BLA, the MD displays almost immediate electrographic discharges (Sloan et al., 2011). Consistent with these anatomical and neurophysiological findings, microinjection of the GABA-A receptor agonist muscimol into the MD attenuates seizures evoked from each of these areas. However, the functional role of specific efferent and afferent pathways linking the MD to these ictogenic regions have not been directly manipulated in the context of seizures. This level of circuit resolution, while unattainable with focal pharmacological manipulations, is now possible using new-generation techniques. We have recently reported that chemogenetic silencing of a large region of the midline and intralaminar thalamus was sufficient to block amygdala kindled seizures. Here, we employed chemogenetics to examine investigate the specific role of the MD and its direct input from the BLA in seizures originating from the BLA. Male, Sprague-Dawley rats were injected with virus (AAV-hSyn-hM4Di) into the MD, and implanted with a stimulating electrode in the BLA; a subset of animals also received a cannula placed bilaterally into the MD to allow for focal delivery of the DREADD agonist, clozapine-N-oxide (CNO). Following systemic administration of CNO (5 mg/kg), amygdala kindled seizures were significantly decreased in severity ($p=0.03$) and duration ($p<0.001$). To directly target and manipulate the projection from the BLA to the MD, we microinjected 500 pmol of CNO in 0.2 µl. In this manner, projections from BLA to MD, but not from BLA to other brain regions were silenced. We found a significant decrease in seizure score ($p=.02$) and duration ($p=0.005$) following bilateral focal silencing of BLA to MD projections. We also found an attenuation of seizure score ($p=0.03$) and duration ($p=0.03$) after silencing of the MD ipsilateral to the stimulating electrode. These data show that silencing of the MD or silencing of the direct projection from the BLA to the MD, is sufficient to attenuate amygdala kindled seizures. This suggests that direct, rather than indirect, propagation of activity from BLA to MD is critical in limbic ictogenesis. The specificity of projection-level targeting may have a translational utility and provides further opportunity to dissect the role of the MD in seizure propagation.

Disclosures: E. Wicker: None. **P.A. Forcelli:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.05/L5

Topic: B.11. Epilepsy

Support: NGMS T32 Fm007055

Title: Hypoxic activation of midline thalamus

Authors: *K. A. SALVATI, M. P. BEENHAKKER
Dept. of Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: Childhood Absence Epilepsy (CAE) is the most common pediatric epilepsy. A striking feature of CAE is the unassailable ability to trigger seizures by hyperventilation. The mechanism(s) underlying hyperventilation-induced seizures is unknown. However, insight into hyperventilation-induced absence seizures will lead to more efficacious treatments than the current, ill-favored anti-epilepsy drugs. Our lab demonstrates that hyperventilation-induced seizures are inducible in the WAG/Rij rat, a rodent model of CAE. Moreover, immunohistochemistry and *in situ* hybridization data reveal *c-fos* expression in the midline thalamus after exposure to 30min of hypoxia to induce hyperventilation. Indeed, thalamocortical circuits are intimately associated with CAE. Identification of *c-fos* positive cells in the midline thalamus is a novel finding and provides us a first glance into understanding how hyperventilation modulates thalamocortical activity to produce absence seizures. Long-standing evidence demonstrates that the midline thalamus has diffuse projections throughout the cortex, as well as reciprocal connectivity with the reticular thalamic nucleus (RT). Additionally, our *c-fos* data highlights an active population of midline cells during hypoxia-induced seizures. We hypothesize that the midline exerts a strong modulatory tone within intrathalamic and thalamocortical circuits, making the midline a likely critical node for the generation of spike-and-wave discharges (SWDs), the electrical signature of absence seizures. To determine how the midline modulates SWD activity, we performed *in vivo* optogentic and EEG experiments to assess SWD expression upon light-induced activation and silencing of midline neurons. In investigating how midline projections alter RT neuron activity, we performed combined patch-clamp and optogentic experiments in acute brain slices. All experiments were conducted using the rodent model of absence epilepsy, the WAG/Rij rat.

Disclosures: K.A. Salvati: None. **M.P. Beenhakker:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.06/L6

Topic: B.11. Epilepsy

Support: Swiss National Foundation grant # 323530_158125

Title: Large scale 4 Hz oscillations control the expression of neocortical fast-ripples in hippocampal sclerosis

Authors: *L. SHEYBANI[1], P. VANMIERLO[1], M. BAUD[2], S. VULLIEMOZ[2], M. SEECK[2], C. MICHEL[1,3,2], C. QUAIRIAUX[1]
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Abstract: A conceptual shift in our understanding of focal epilepsy has led to the recognition that epileptic networks (EN), and not solely the localized brain region named “epileptic focus” (EF), are major pathogenic factors of the disease. However, how large-scale EN recruit distant pathological nodes, and whether this promotes the emergence of pathological activities remote from the focus remain largely unknown. Here, we show that neocortical fast-ripples (FRs) are generated in hippocampal sclerosis and are triggered by large-scale synchronizing 4-Hz waves that start in both hippocampi and then spread to frontal regions. These slow oscillations constrain bursts of paroxystic 20-30 Hz activity to which neocortical FRs are time-locked. We further show that the mechanism through which slow oscillations favor the generation of FRs might be through a modulation of neuronal firing, as we observed a strong phase-coupling of action potentials over the 4-Hz phase during these events. These low- and high-frequency coupling mechanisms demonstrate an intriguing parallel with cross-frequency coupling observed in certain physiological brain functions. Thus, similar mechanisms might underlie normal and pathological brain functions that rely on large-scale physiological or pathological networks.

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Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.07/L7

Topic: B.11. Epilepsy

Support: NIH grant 1R01NS094550

Title: Laminar distribution of ultra high frequency oscillations in the epileptic brain induced by focal cortical dysplasia in mice

Authors: *Q.-Q. SUN[1], A. WILLIAMS[2]
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Abstract: Abstract The epileptic brain is often associated with the presence of high frequency oscillations (HFOs, >25 Hz) that have recently gained attention as potential biomarkers to help define the cortical seizure zone. Here we evaluate the aberrant spectral architecture and spatial distribution of HFOs associated with spontaneous spike-wave discharge (SWD) patterns in an experimental model of focal cortical dysplasia (FCD) induced by neonatal freeze lesions (FLs) to the right S1 cortex. Chronic bipolar recordings from awake, behaving animals indicated a high prevalence of spontaneous SWDs in 83% (10/12) of animals exposed to the FL injury as evaluated at 5-11 months of age. SWDs were associated with a strong increase in HFOs locked to the spike/wave seizure pattern and largely confined to the ipsilateral cortex near the site of the FL injury. Additional acute recordings with linear micro-electrode arrays were obtained to evaluate laminar differences in HFOs during spontaneous periods of hyper-excitable burst-suppression activity under general anesthesia. FL animals exhibited significant increases in spontaneous HFOs that were confined to granular and supragranular layers with a concomitant increase in unit activity while control animals exhibited minimal changes in 'ultra-high' frequency responses above 100 Hz (i.e. ripple waves). Spike sorting of well-isolated single-units from FL cortex indicated a differential expression pattern of putative excitatory (EXC) versus inhibitory (INH) cells. EXC cells were predominately observed in the outer cortical layers and showed only weak association with HFOs while the deeper INH units were strongly phase-locked to ripple oscillations (100-500 Hz). The spontaneous cyclic spiking of cortical inhibitory cells appears to be the driving substrate behind HFOs and may prove useful in identifying regions of hyperexcitable tissue in the epileptic brain. In summary, the current studies indicate a strong prevalence of HFO activity in a model of FCD that are 1) mainly confined to the injured cortex, 2) originate in the upper cortical layers, 3) are most prominent during high-amplitude 'spike' deflections of the local field potential, and 4) indicate strong phase-locking to putative INH cells predominately within the supragranular layers of the malformed cortex. As demonstrated in the current study, the utilization of commercially available electrode arrays offers a powerful high-resolution tool for mapping the cortical circuitry of seizurogenic tissue and identification of key cellular markers underlying brain hyperexcitability and may help guide clinical diagnosis and treatment of the epileptic brain.

Disclosures: Q. Sun: None. **A. Williams:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.08/L8

Topic: B.11. Epilepsy

Support: 1R01NS097762-01

Title: The superior colliculus is a site for anticonvulsant action for cannabinoid agonists

Authors: *R. HAMMACK[1], V. R. SANTOS[2], E. WICKER[1], P. N'GOUEMO[4], P. A. FORCELLI[3]
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Abstract: Despite growing evidence for anticonvulsant properties of drugs targeting the cannabinoid system (e.g., CB_1 receptor agonists), the site of anticonvulsant action of these drugs remains unknown. CB_1 receptors are expressed in high density in limbic structures such as the hippocampus, as well as in components and targets of the basal ganglia. One area of the brain with a large number of these receptors is the deep and intermediate layers of the superior colliculus (DLSC). The DLSC receives inhibitory input from the substantia nigra pars reticulata, another region with high density of CB_1 receptors. These latter structures are of particular interest because activation of the DLSC or inhibition of the SNpr display broad-spectrum anticonvulsant effects. Since CB_1 receptors have been shown to preferentially target both presynaptic and inhibitory synapses, activation of these G_i coupled receptors would hypothetically cause disinhibition of DLSC and thus an anticonvulsant effect. To test this hypothesis, we employed two rat models of seizures: (1) focally evoked limbic seizures triggered by microinjection of bicuculline into the “Area Tempestas” (AT) and (2) audiogenic seizures evoked in genetically epilepsy prone rats (GEPR-3). Using a within-subject design, we microinjected the CB_1 agonist CP 55,490 (26.5 nmol in 0.5 µl) or vehicle in into the DLSC prior to evoking seizures. In the AT model, we found that microinjection of CP 55,490 significantly decreased the severity of seizures compared to vehicle injection ($P=0.016$). Moreover, the number of limbic motor seizures that occurred during the one hour observation was significantly decreased by CP 55,490 ($P=0.0007$). In the GEPR model, CP 55,490 microinjection likewise decreased the severity of evoked seizures ($P=0.031$). These data suggest that activation of CB_1 receptors within the DLSC is sufficient to produce anticonvulsant effects. Studies are currently underway to determine if activation of these receptors is necessary for the anticonvulsant effects of systemically administered CB agonists, and to determine the effect of CB agonists on synaptic transmission within the DLSC.

Disclosures: R. Hammack: None. **V.R. Santos:** None. **E. Wicker:** None. **P. N'Gouemo:** None. **P.A. Forcelli:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.09/L9

Topic: B.11. Epilepsy

Support: Epilepsy Research UK

Title: Cortical macrostructure influences the spread of epileptiform activity

Authors: *R. R. PARRISH, A. OFFER, C. RACCA, A. J. TREVELYAN
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Abstract: Seizures are the defining feature of epilepsy. They typically arise in a discrete focus in the brain and then propagate to surrounding regions; exactly how seizures propagate, however, and what endogenous mechanisms exist to resist this spread, are poorly understood. Previous work, from multiple groups, has demonstrated the presence of a powerful initial inhibition ahead of the ictal wave front. Nevertheless, it remains unclear how cortical areal boundaries and layers may influence the propagation. We therefore examined this issue, using low magnification Ca^{2+} network imaging (GCaMP6f, 2.5x objective) of spreading epileptiform activity. We performed Ca^{2+} network imaging while simultaneously recording extracellular local field potentials at two locations, flanking the area 17/18 cortical boundaries. Epileptiform activity was induced by bathing brain slices in 0 Mg^{2+} artificial cerebro-spinal fluid (ACSF).
As described by many researchers, the 0 Mg^{2+} model displays a variety of pathological discharge patterns, but in this study, we focused on propagation of full ictal events (IEs), which are characterised by a wavefront of intense neuronal firing, probably incorporating all neurons locally, and followed typically by rhythmic discharges, very similar to that seen in vivo during tonic-clonic seizures. Early IEs propagate slower than later ones. These early events preferentially spread in the deep laminar layers, with a higher number of initial IEs in each slice appearing in the deep laminar layer over the superficial. Consequently, the propagation speed during IEs in the deep layer is also generally faster. No medio-lateral directionality preference was seen in propagating IEs and on occasions, we observed successive events propagating in opposite directions, suggesting that the same circuits are responsible for propagation regulation in both directions. In all cases, propagation was not steady, but rather proceeded in episodic steps across the network. Our imaging was centred on primary visual cortex, because the borders of this area are reasonably well defined in adult mice using immunohistochemical markers. We observed instances where the seizure spread paused in the middle of area 17, and also close to the areal boundaries. Slices were fixed, and prepared for histological examination of these boundaries. We will present these analyses at the meeting. These studies will shed light into how

seizures spread through cortical tissue and allow for us to then study how neocortical anatomy contributes to propagation, delay, and restraint of seizure activity.

Disclosures: R.R. Parrish: None. **A. Offer:** None. **C. Racca:** None. **A.J. Trevelyan:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.10/L10

Topic: B.11. Epilepsy

Support: NCRR (S10RR014978)

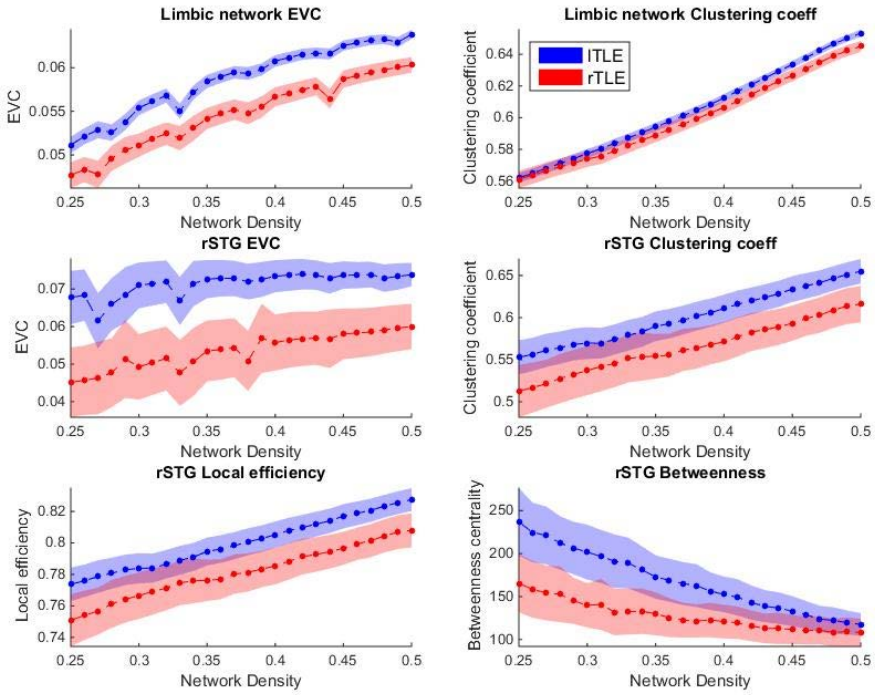
NIH (S10RR031599, R01-NS069696, 5R01-NS060918, U01MH093765)

Title: Graph theoretic analysis of limbic subnetwork in left vs right temporal lobe epilepsy

Authors: *S. SUBRAMANIAN[1], N. PELED[1], R. L. GOLLUB[3,1], M. HIBERT[1], L. DOUW[1], S. M. STUFFLEBEAM[2]
[1]Radiology, [2]MGH Martinos Ctr., Charlestown, MA; [3]Psychiatry, MGH, Charlestown, MA

Abstract: Purpose: To investigate differences in limbic network functional connectivity between left and right temporal lobe epilepsy (TLE) on a large data set of patients using graph theory.
Methods: Interictal resting state fMRI was performed in 81 left and 33 right TLE patients. Functional connectivity networks were constructed based on the Lausanne 2008 parcellation (from Connectome mapper) of 219 cortical surface regions using Pearson correlation. These networks were thresholded at a range of biologically plausible connection densities (25-50%) and graph theoretic properties were computed, including betweenness centrality, clustering coefficient, local and global efficiency, and eigenvector centrality (EVC). A subset of 52 bilateral limbic network regions (anterior cingulate, posterior cingulate, fusiform, entorhinal, orbitofrontal, insula, parahippocampus, superior temporal) was selected based on a priori knowledge, and the distributions of graph theoretic properties for these regions was computed for left and right TLE with 95% confidence intervals (CI). The mean values of all graph properties for the overall limbic subnetwork were also computed for left and right TLE with 95% confidence intervals. Regional and global limbic subnetwork distributions were examined for differences between left and right TLE, as evidenced by non-overlapping 95% CI for at least 20% of the densities analyzed.
Results: Global properties show that patients with left TLE have higher clustering coefficient and EVC across the limbic subnetwork than those with right TLE. Upon examination of individual sub-regions, the right superior temporal gyrus (rSTG) shows significant differences between right and left TLE across multiple metrics and densities. Overall, patients with right TLE have

lower EVC, clustering coefficient, local efficiency, and betweenness centrality in the rSTG than those with left TLE.
Conclusions: Graph theoretic analysis reveals limbic subnetwork differences between left and right TLE at resting state that may have important diagnostic and prognostic implications.



Disclosures: S. Subramanian: None. **N. Peled:** None. **R.L. Gollub:** None. **M. Hibert:** None. **L. Douw:** None. **S.M. Stufflebeam:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.11/M1

Topic: B.11. Epilepsy

Title: Network origins of epileptic activity

Authors: *S. GHIASVAND[1], Y. BERDICHEVSKY[2]
[1]Lehigh university, Bethlehem, PA; [2]Lehigh Univ., Bethlehem, PA

Abstract: Introduction: Epilepsy is a neurological disorder characterized by recurrent abnormal neuronal activity or seizures. Epilepsy is a multi-scale disease that can be brought about by

changes at the cellular or network level. Currently, the precise network parameters necessary for epileptic behavior are not well defined. We wish to examine particularly the effects of network size (number and density of neurons) and connectivity as a characterization of epileptic network topology. We employ both *in vitro* and computational approaches to vary the network topology and examine the effects on network firing patterns. This investigation will elucidate more effective mechanisms for antiepileptic drugs.
Materials and Methods: The *in vitro* aspect of our study was conducted using organotypic hippocampal slice cultures (OHCs). OHCs have been shown to be an effective model of posttraumatic epilepsy as they become spontaneously epileptic after one to two weeks *in vitro.* We created and cultured OHCs and hippocampal sub-regions (i.e. CA3 and CA1-DG) in order to vary the network size and circuitry. We quantified firing patterns using chronic electrical recordings. Immunohistochemistry was used to quantify neuronal number and density. The computational modeling employed Integrate-and-Fire neurons connected via synapses with short-term depression mechanism in order to examine the effects of network size and synaptic strength on synchronous bursting or seizure propagation.
Results and Discussion: We successfully modeled neuronal networks of different dimensions. We have also begun culturing organotypic slices of hippocampal sub-regions. Electrical recordings from these sub-regions reveal different firing patterns and different rates of development of epileptic behavior. The CA3 sub-region cultures demonstrated a more rapid development of incidence of seizures.
Conclusion: We have developed both computational and *in vitro* models to study the effects of network topology on epileptogenesis. Our results from electrical recordings from OHCs and sub-regions reveal that epileptogenesis is affected by network size and circuitry. These results are also compatible with the results obtained from our network simulation. Combined computational and experimental results may give insights into the network origins of epileptic activity.

Disclosures: S. Ghiasvand: None. **Y. Berdichevsky:** None.

Poster

664. Networks: Thalamus, Cortex, and Brainstem

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 664.12/M2

Topic: B.11. Epilepsy

Support: NIH Grant 5R44NS062477-08

Title: Quantification of seizurogenic activity with multiwell microelectrode array technology for proconvulsant risk assessment

Authors: *D. C. MILLARD, H. B. HAYES, C. A. ARROWOOD, A. M. NICOLINI
Axion Biosystems, Atlanta, GA

Abstract: The lack of advancement in anti-epileptic drugs (AEDs) over the last 30 years, along with the continued need for improved proconvulsant screening in drug safety, motivates the need for new assays of seizurogenic neural activity. Previous work has established an in vitro approach for detecting and quantifying seizurogenic activity using multiwell microelectrode array (MEA) technology, providing a predictive and high-throughput avenue for the evaluation of the efficacy of AEDs and the proconvulsant risk of other drug candidates. Here, we present an updated assay of seizurogenic activity based upon guidelines developed in the HESI NeuTox consortium, which is a collection of academic, commercial, and pharmaceutical representatives working towards the development of in vitro assessment of proconvulsant risk. We used previously published metrics for the detection of burst spiking events and the quantification of synchronization across a neural population, in spontaneous and evoked conditions. Data are included from cryopreserved rat cortical neurons evaluated with the 10 compounds selected by the NeuTox consortium, which include reference compounds with known proconvulsant risk via multiple mechanisms and negative control compounds. Our results support the combined use of evoked and spontaneous neural activity, collected using multi-well MEA technology, for the high throughput evaluation of complex neuronal networks in vitro to quantify the proconvulsant risk of candidate pharmaceuticals in a pre-clinical setting.

Disclosures: D.C. Millard: A. Employment/Salary (full or part-time):; Axion BioSystems, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axion BioSystems, Inc. **H.B. Hayes:** A. Employment/Salary (full or part-time):; Axion BioSystems, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axion BioSystems, Inc. **C.A. Arrowood:** A. Employment/Salary (full or part-time):; Axion BioSystems, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axion BioSystems, Inc. **A.M. Nicolini:** A. Employment/Salary (full or part-time):; Axion BioSystems, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axion BioSystems, Inc..

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.01/M3

Topic: B.11. Epilepsy

Support: NIH Grant AG045656

NIH Grant MH083911

Charles H. Smith Endowment Fund

Title: Gluconate inhibition of CLC-3 chloride channels as a novel treatment for neonatal seizure

Authors: *Z. WU
Huck Life Sci., University Park, PA

Abstract: Neonatal seizure is different from adult seizure, and many antiepileptic drugs that are effective in adults often fail to treat neonatal seizure. Here, we report that gluconate inhibits neonatal seizure by blocking CLC-3 chloride channels. We discover a voltage-gated outward rectifying Cl^- current mediated by CLC-3 Cl^- channels in early developing brains but not in the adult brains. Blocking CLC-3 Cl^- channels by gluconate inhibits seizure activity both in neonatal brain slices and in neonatal animals. Consistently, neonatal neurons in the CLC-3 knockout mice lack the outward rectifying Cl^- current and show reduced epileptiform activity upon stimulation. Mechanistically, we demonstrate that activation of CLC-3 Cl^- channels may alter intracellular Cl^- homeostasis and enhances GABA excitation. Our study identifies gluconate as a novel antiepileptic drug to treat neonatal seizures through inhibiting CLC-3 Cl^- channels.

Disclosures: Z. Wu: None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.02/M4

Topic: B.11. Epilepsy

Title: Effect of levetiracetam treatment on neurotransmission in the dentate gyrus of rats with temporal lobe epilepsy

Authors: *L. PICHARDO-MACIAS[1,2], B. A. RAMÍREZ[3], K. B. SÁNCHEZ- HUERTA[2], I. J. CONTRERAS[2], M. S. NAVARRETE[2], E. M. GARCÍA[2], S. R. ZAMUDIO[4], J. L. CHAVEZ[3], J. G. MENDOZA-TORREBLANCA[2]
[1]Inst. Politecnico Nacional, México, Mexico; [2]Neurociencias, [3]Farmacología, Inst. Nacional de Pediatría, México D.F., Mexico; [4]Lab. de Neurociencia conductual I, Inst. Politécnico Nacional, México D.F., Mexico

Abstract: Temporal lobe epilepsy (TLE) is characterized by the appearance of epileptic foci in limbic structures, particularly in the hippocampal formation. Three fundamental pathophysiological features have been described in this condition: an imbalance between inhibition-excitation, hyper-excitability and neuronal hyper-synchrony. Levetiracetam (LEV) is an anticonvulsant drug with a unique profile of activity that results in a decrease of spontaneous recurrent seizures (SRZ). The exact mechanism by which LEV reduces SRZ is still unknown, but its mechanism of action may involve effects on neurotransmitter release. It is not clear whether

these effects include excitatory or inhibitory neurotransmission or both, since LEV´s primary target, the synaptic vesicle protein 2A, is ubiquitously expressed in nearly all types of synaptic vesicles. Therefore, the objective of the present study was to evaluate the effects of LEV on inhibitory and excitatory neurotransmission of the dentate gyrus (a region with major synaptic changes during TLE). For this purpose, male Wistar rats were divided into the following groups: a) control, b) control + LEV, c) epileptic and d) epileptic + LEV. TLE was generated by the systemic administration of lithium and pilocarpine, seizure scores were determined by behavioral analysis of videotapes. LEV treatment lasted one week (300 mg / kg / d) and was done by osmotic minipumps. The animals were implanted with a cannula in the dentate gyrus, then 14 dialysate samples were collected using microdialysis. The amino acids contained in the dialysates were quantified by high performance liquid chromatography (HPLC) coupled to fluorometric detection. The extracellular concentration of each amino acid (GABA, glutamate, aspartate, glutamine, taurine and glycine) was measured under basal conditions as well as in the presence of a depolarizing stimulus that consisted of the application of a high potassium solution (100 mM). TLE caused an imbalance between excitatory and inhibitory neurotransmitter systems in the dentate gyrus. Treatment with LEV increased the concentration of GABA, tending to restore the lost balance; a mechanism by which it could also reduce epileptic seizures.

Disclosures: L. Pichardo-Macias: None. **B.A. Ramírez:** None. **K.B. Sánchez- Huerta:** None. **I.J. Contreras:** None. **M.S. Navarrete:** None. **E.M. García:** None. **S.R. Zamudio:** None. **J.L. Chavez:** None. **J.G. Mendoza-Torreblanca:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.03/M5

Topic: B.11. Epilepsy

Support: NIH Grant NS097726

Title: Epileptic circuits revealed using EpiPro, a novel synthetic activity-modulated promoter

Authors: *C. T. BURKE[1], I. VITKO[1], A. GAWDA[1], J. KIM[1], K. BRODIE[1], K. SULLIVAN[1], B. WALKER[1], M. OTTOLINI[2], D. PEREZ-REYES[1], J. KAPUR[3], M. PATEL[2], E. PEREZ-REYES[1]
[1]Pharmacol., [2]Anesthesiol., [3]Neurol., Univ. of Virginia, Charlottesville, VA

Abstract: Temporal lobe epilepsy (TLE) is a disease in which seizures originate in the hippocampus (or parahippocampal structures) and can spread throughout the brain. We have developed an activity modulated synthetic promoter (“EpiPro”) that contains the response elements of transcription factors known to be upregulated in patients with epilepsy. To map the

epileptic circuit in a rat model of TLE, an adeno-associated virus (AAV) with EpiPro driving GFP was injected into the temporal lobes of epileptic and naïve rats. Expression in naïve animals was low, with the exception of Mossy cells inside the dentate hilus and subsets of subicular neurons. In animals induced to have spontaneous recurring seizures with lithium-pilocarpine, there was large activation of dentate granule cells, and modest activation of subicular neurons. These subicular neurons projected throughout the brain, and likely explain how seizures spread from the hippocampal focus. These findings provide in vivo evidence to support the "dentate gate breakdown" hypothesis. Our data also validates the use of EpiPro to selectively drive gene therapies in epileptic neurons.

Disclosures: C.T. Burke: None. **I. Vitko:** None. **A. Gawda:** None. **J. Kim:** None. **K. Brodie:** None. **K. Sullivan:** None. **B. Walker:** None. **M. Ottolini:** None. **D. Perez-Reyes:** None. **J. Kapur:** None. **M. Patel:** None. **E. Perez-Reyes:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.04/M6

Topic: B.11. Epilepsy

Support: H2020-Marie Sklodowska Curie Individual Fellowship (No. 70141)

Medical Research Council

Wellcome Trust

Title: Closed-loop gene therapy for intractable focal epilepsy

Authors: *A. LIEB, Y. QIU, C. DIXON, D. M. KULLMAN
Clin. and Exptl. Epilepsy, UCL / Inst. of Neurol., London, United Kingdom

Abstract: Around 50 Million people worldwide are affected by epilepsy, of whom 20% do not respond to commonly available drugs. New drug development is limited by difficulties in differentiating between neurons involved in seizure generation and normal brain function. Many antiepileptic drugs show a relatively narrow therapeutic window and elicit a variety of serious side-effects, mainly because they affect the whole brain. The only effective treatment option for focal-onset refractory epilepsy to date is surgical resection, which is often restricted by the proximity to eloquent cortex. Recent research has focused on controlling epileptic seizure activity on demand by i) optogenetics, ii) chemogenetics, iii) electrical stimulation, iv) focal cooling, or v) targeted drug-delivery. However, all these approaches are limited in their translational applicability. In contrast to these approaches, we propose a closed-loop method for biochemical detection and ion-channel based suppression of epileptic seizures.

We created a viral construct which was initially biophysically characterized by heterologous overexpression in Neuro-2A-cells and whole-cell patch-clamp recordings. Subsequently, it was evaluated in the acute chemoconvulsant induced model of epilepsy, where it showed particular effectiveness in reducing spike-wave complexes occurring at 4-14Hz (associated with motor convulsions), the absolute number of spikes, and the cumulative coastline. In addition we demonstrated the efficiency of the viral construct in reducing the total number of spontaneously generated epileptic seizures in the chronic Tetanus Toxin induced model of focal refractory epilepsy.
In this work we propose a novel closed-loop gene therapeutic approach, able to biochemically detect and inhibit seizure generation in generalization. This novel approach presents the first autoregulatory gene-therapeutic strategy targeting intractable focal epilepsy.

Disclosures: **A. Lieb:** None. **Y. Qiu:** None. **C. Dixon:** None. **D.M. Kullman:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.05/M7

Topic: B.11. Epilepsy

Title: Transcranial near-infrared laser treatment suppresses pentylenetetrazol-induced severe seizure behaviors and status epilepticus in developing rats

Authors: *C.-M. TSAI[1], S.-F. CHANG[1], H. CHANG[3,2]
[1]Grad. Inst. of Med. Sciences, Col. of Med., [2]Pediatrics, Sch. Of Med., Taipei Med. Univ., Taipei, Taiwan; [3]Dept. of Pediatrics, Taipei Med. Univ. Hosp., Taipei, Taiwan

Abstract: OBJECTIVE To evaluate effects of transcranial near-infrared laser treatment (NILT) on subcutaneous pentylenetetrazole (scPTZ)-induced seizure behaviors and SE in developing rats. **METHODS** Sprague-Dawley rats aged postnatal day 30-36 were divided into NILT group and sham group. We injected PTZ (90 mg/kg) subcutaneously to rats in each group and applied gallium-aluminum-arsenide diode laser to rats in the NILT group transcranially prior to PTZ injections. We staged the intensities of seizures to mild, moderate, and severe seizures based on “revised Racine’s scale” with minor modifications. The seizures were evaluated with parameters including total duration of seizures (TDs), percentage time in seizures (PTs), maximum seizure stages per five minutes (Max), “weighted seizure score” (W), in which stage and duration were weighted, and latency to seizures (Ls). The SE, modified from Sato SM and Woolley CS’s definition, was evaluated with percentage of rats developed SE (PRSE), total duration of SE (TDSE), percentage time in SE (PTSE), and latency to SE (LSE). We analyzed the results of PTs, Max, W, PRSE, and PTSE with repeated measures two-way ANOVA, and unpaired t test for data of TDs, Ls, TDSE, and LSE. **RESULTS** The total duration of severe seizures was

significantly shorter and percentage time in severe seizures was significantly lower in the NILT group ($p<0.05$) compared to those in the sham group. As for mild and moderate seizures, there was no significant difference either evaluated with TDs or PTs. The data of PTs, Max, and W were lower in the NILT group ($p<0.05$). PRSE was significantly lower in the NILT group ($p<0.01$), also significantly shorter TDSE and significantly lower PTSE were detected in the NILT group ($p<0.05$). There was no significant difference in terms of LSE or Ls.
CONCLUSION Our findings show that transcranial NILT reduces durations and severities of scPTZ-induced severe rather than mild or moderate seizure behaviors and the incidence and durations of SE in developing rats. This is the first report demonstrating the effectiveness of transcranial NILT on PTZ-induced seizure behaviors and especially on suppressing SE, and this might shed light on the application of transcranial NILT for children with convulsive status epilepticus.

Disclosures: C. Tsai: None. **S. Chang:** None. **H. Chang:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.06/M8

Topic: B.11. Epilepsy

Support: Xenon Pharmaceuticals

Title: Selective inhibition of $Na_V1.6$ drives anticonvulsant efficacy in mouse models of epileptic encephalopathy ($SCN8A^{N1768D+/-}$) and adult partial onset seizures (maximal electroshock)

Authors: C. M. DUBE[1], P. KARIMI TARI[1], M. WALDBROOK[1], K. NELKENBRECHER[1], J. MARK[1], T. FOCKEN[2], N. SHUART[3], K. KHAKH[3], R. WINQUIST[4], J. EMPFIELD[2], C. J. COHEN[3], *J. JOHNSON, JR[5]
[1]In Vivo Pharmacol., [2]Chem., [3]Cell. & Mol. Biol., [4]Translational Res., Xenon Pharmaceuticals Inc., Burnaby, BC, Canada; [5]Cell. & Mol. Biol., Xenon Pharmaceuticals, Burnaby, BC, Canada

Abstract: Voltage-gated sodium channel inhibitors are commonly used as anti-epileptic drugs for treating patients with partial and tonic-clonic seizures. While effective for some patients, these drugs are non-selective among Na_V's and are dose limited by their adverse effects. Decreased expression of $Na_V1.1$ in inhibitory interneurons can cause seizures, as in Dravet syndrome, so the off-target activity of non-selective antagonists may work at cross-purpose to the intended effect. Excitatory pathways in the CNS are preferentially mediated by $Na_V1.6$, and missense mutations of SCN8A cause gain-of-function $Na_V1.6$ channels leading to a rare form of severe childhood epilepsy (Early Infantile Epileptic Encephalopathy 13, EIEE13). We have developed highly selective $Na_V1.6$ inhibitors that spare all other Na_V isoforms and others that

selectively inhibit both $Na_V1.6$ and $Na_V1.2$ but spare $Na_V1.1$. We tested these selective compounds in two mouse models of seizures, a 6Hz psychomotor seizure assay in $Na_V1.6$ transgenic mice ($N1768^{D/+}$) and the maximal electroshock (MES) assay in wild type mice. Selective $Na_V1.6$ inhibitors prevented induced seizures in EIEE13 mice. Anticonvulsant activity was well correlated with inhibition of $Na_V1.6$ and independent of inhibit of $Na_V1.1$ or $Na_V1.2$. The same was true in the MES assay with mice that lack mutant sodium channels ($p<0.05$). These data suggest that the primary driver of efficacy for selective and non-selective Na_V inhibitors in both $SCN8A^{N1768D/+}$ and wild type mice is inhibition of $Na_V1.6$. This implies that selectively targeting $Na_V1.6$ could confer anti-seizure efficacy while sparing off-target activities. We anticipate that eliminating inhibition of the sodium channel isoforms not necessary for efficacy, particularly $Na_V1.1$ and $Na_V1.5$, will lead to better tolerated and more efficacious treatments for patients with epilepsy.

Disclosures: C.M. Dube: A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **P. Karimi Tari:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **M. Waldbrook:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **K. Nelkenbrecher:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **J. Mark:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **T. Focken:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **N. Shuart:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **K. Khakh:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **R. Winquist:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **J. Empfield:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **C.J. Cohen:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **J. Johnson:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.07/M9

Topic: B.11. Epilepsy

Support: NIH Grant R0-1NS096976-02

Dravet Syndrome Foundation A128618

Title: Targeted discovery and development of serotonin modulators for Dravet syndrome

Authors: *A. GRIFFIN[1], K. R. HAMLING[1], K. KNUPP[3], P. JAISHANKAR[2], A. R. RENSLO[2], S. C. BARABAN[1]
[1]Neurolog. Surgery, [2]Dept. of Pharmaceut. Chem. and Small Molecule Discovery Ctr., Univ.

California San Francisco, San Francisco, CA; [3]Dept. of Pediatrics, Univ. of Colorado Denver, Denver, CO

Abstract: Dravet syndrome is a catastrophic childhood epilepsy often caused by genetic mutations in the voltage-gated sodium channel *SCN1A*. Currently available antiepileptic drugs do not offer adequate seizure control for these patients; therefore there is a significant need for the discovery and development of new therapies. Zebrafish larvae with a mutation in homologous sodium channel gene, *scn1lab,* recapitulate the spontaneous seizure activity and mimic the convulsive behavioral movements observed in Dravet syndrome. Importantly, *scn1lab* mutant zebrafish also show pharmacoresistance to several antiepileptic drugs, emulating the persistent drug resistant seizures observed in human patients (Baraban et al. 2013; Dinday and Baraban, 2016). Using *scn1lab* mutant zebrafish larvae, we developed an in vivo drug screening platform to identify potential antiepileptic compounds. In a blind screen of more than 3000 drugs, the 1st generation antihistamine clemizole was identified as having potent antiepileptic properties. Further characterization of clemizole revealed novel binding to the serotonin receptors HTR2A and HTR2B in addition to its known binding to the histamine H1 receptor. Structure-activity relationship studies were performed using clemizole as our hit compound. Using medicinal chemistry we synthesized a library of 28 clemizole analogs with favorable drug-like properties. These 'clemalogs' aimed to improve the antiepileptic activity of clemizole by enhancing the HTR2 receptor activity. Three novel clemalogs were identified as capable of suppressing the convulsive seizure behaviors in our zebrafish drug screening platform. Furthermore, pharmacological analysis using radioligand binding assays confirmed strong binding affinities to human HTR2 receptors. In addition to developing clemalogs, a targeted screen of 65 of FDA approved serotonin modulating compounds was performed. Two 5HTR2 agonists, lorcaserin and trazodone, were identified as mimicking the antiepileptic activity of clemizole in *scn1lab* larvae. Under a compassionate use off-label program we treated five Dravet syndrome patients with lorcaserin (Belviq). All patients reported an initial reduction in seizure activity confirming our preclinical zebrafish data (Griffin et al. 2017). We conclude zebrafish-based drug discovery and development confirms a role for the modulation of serotonin signaling as an effective antiepileptic treatment for Dravet syndrome.

Disclosures: A. Griffin: None. **K.R. Hamling:** None. **K. Knupp:** None. **P. Jaishankar:** None. **A.R. Renslo:** None. **S.C. Baraban:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EpyGenix Therapeutics. F. Consulting Fees (e.g., advisory boards); EpyGenix Therapeutics.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.08/M10

Topic: B.11. Epilepsy

Support: Inter-Agency Agreement between NIH/NINDS (Y1-O6-9613-01) and USAMRICD

NIH CounterACT

Research Participation Program for the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and U.

Title: Assessment of midazolam and diazepam to treat nerve agent-induced seizures in pediatric and adult rats

Authors: K. HAINES[1], E. N. DUNN[2], L. M. MATSON[2], C. ARDINGER[2], H. S. MCCARREN[2], S. M. MILLER-SMITH[2], *J. H. MCDONOUGH, Jr.[1]
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Abstract: Chemical warfare nerve agents like sarin (GB) and VX cause severe central nervous system effects, the most devastating of which is a state of prolonged seizures known as status epilepticus. In a civilian nerve agent exposure situation, children would likely be among the worst casualties as they are more susceptible than adults to seizures (Haut et al., 2004; Rakhade & Jensen, 2009; Sidell et al., 2008). The current study compared the anticonvulsant efficacy of midazolam and diazepam in male and female pediatric and adult rats. We determined the median effective dose (ED_{50}) and the incidence of seizure at one and four hours post-treatment to inform future clinical treatment of nerve agent-induced seizures across age groups. Female and male postnatal day (PND) 21, 28, and 70 rats were implanted with electroencephalographic (EEG) electrodes to monitor seizure activity. Animals were exposed to the nerve agents GB or VX and then treated five minutes after seizure onset with either midazolam or diazepam. The up-down method (Dixon & Massey, 1983) was used to determine the anticonvulsant ED_{50} for each sex, agent, and age group. Based on the ED_{50} confidence intervals, PND21s exposed to VX had lower midazolam and diazepam ED_{50} values than adults. There were no clear age differences in animals exposed to GB, but the results suggest that PND21 males had a lower ED_{50} value for diazepam compared to other age groups. We also observed a significant change in incidence of seizure for animals treated with midazolam between one hour (42.3%) and four hours (46.8%), $\chi^2_{(1)} = 5.00$, $p = .041$, $OR = 3.0$ [95% CI: 1.09, 8.25]. This was seen most frequently in PND21s, although no significant differences between the age groups were found. In conclusion, ED50 values for midazolam were similar across age groups, suggesting that a similar treatment dose may be effective across all age groups. Because there was a greater variability in the doses of diazepam across age groups, midazolam may be the better treatment option for nerve agent-induced seizures to be used in a mass casualty situation involving both pediatric and adult populations. However, its effects are only temporary because some animals had seizure activity

at four hours. Experiments are currently ongoing to determine if either treatment protects susceptible brain regions from neuronal loss.

Disclosures: K. Haines: None. **E.N. Dunn:** None. **L.M. Matson:** None. **C. Ardinger:** None. **H.S. McCarren:** None. **S.M. Miller-Smith:** None. **J.H. McDonough:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.09/N1

Topic: B.11. Epilepsy

Support: CSIR, India vide project MLP 0039

Title: Investigating the antiepileptic potential of mycophenolate mofetil in a rat model of temporal lobe epilepsy

Authors: *A. G. MAZUMDER, V. PATIAL, D. SINGH
CSIR-Institute of Himalayan Bioresource Technol., Palampur, India

Abstract: Traumatic brain injuries in case of temporal lobe epilepsy gives rise to the emergence of several neuroinflammatory mediators which cause excitotoxicity and severe neuronal impairment. Mycophenolate mofetil, commonly used as an immunosuppressant, has been widely used in various organ transplantations across the globe. However, its neuroprotective effects have been reported in several preclinical and clinical studies. The present work was envisioned to explore the effects of mycophenolate mofetil on seizure severity and aggressive behavior in a rat model of lithium-pilocarpine-induced spontaneous recurrent seizures. Male wistar rats were randomly divided into different groups, and were subjected to lithium pilocarpine induced status epilepticus method, following the drug treatment. The rats were treated for 28 days with mycophenolate mofetil at different doses, 28 days after induction of seizures. The behavior of the rats were video recorded for 72 h prior to the end of treatment for seizure severity score and the aggressive behavior was evaluated using various behavior paradigms such as, approach response test, touch response test and pick up test. These results showed that treatment with the drug distinctively reduced lithium-pilocarpine instigated spontaneous recurrent seizures severity score with reduced aggression like behavior. These findings concluded that mycophenolate mofetil has antiepileptic effect and it reduces seizure linked aggressive behavior.

Disclosures: A.G. Mazumder: None. **V. Patial:** None. **D. Singh:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.10/N2

Topic: B.11. Epilepsy

Support: Boston Children's Hospital Translational Research Program

Biscayne Neurotherapeutics

Title: Traumatic brain injury alters Huperzine-A cerebral pharmacodynamics

Authors: *U. DAMAR[1], R. GERSNER[1], J. JOHNSTONE[2], K. KAPUR[1], S. COLLINS[2], S. C. SCHACHTER[3], A. ROTENBERG[1]
[1]Neurol., Boston Children's Hosp., Boston, MA; [2]Biscayne Neurotherapeutics, Miami, FL; [3]Neurol., Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: Introduction: Traumatic brain injury (TBI) may affect the pharmacodynamics of centrally acting drugs. Paired-pulse transcranial magnetic stimulation (ppTMS) a safe and noninvasive measure of cortical GABA-mediated cortical inhibition. Huperzine A (HupA) is a naturally-occurring acetylcholinesterase inhibitor with newly discovered potent GABA-mediated antiepileptic capacity, which is reliably detected by ppTMS. To test whether TBI alters cerebral HupA pharmacodynamics, we exposed rats to fluid percussion injury (FPI), and tested whether ppTMS metrics of cortical inhibition differ in magnitude and temporal pattern in injured rats.
Methods: Anesthetized adult rats were exposed to FPI or sham injury, and treated with either saline or HupA. 90 minutes following the injury, rats were injected with HupA or saline (0.6 mg/kg, i.p.). Cortical inhibition was measured by 15 paired pulses immediately before the injections at baseline, and then every 15 minutes for 90 minutes post-injection. Log transform of the test:conditioning ratio of the motor evoked potential (MEP) amplitudes were compared across treatment conditions. Repeated Measures ANOVA was used to compare saline and HupA in both sham and TBI groups. Mann Whitney U test was used to compare TBI and sham groups regarding baseline cortical inhibition and the time to maximum HupA effect. To compare time to maximal HupA effect, we also adopted a longitudinal model using linear mixed-effects regression model, and included linear and quadratic effects of time and their interaction with group to differentiate the trajectories of sham and TBI groups.
Results: TBI resulted in reduced cortical inhibition 90 minutes after the injury compared to sham controls ($p=0.03$). HupA enhanced cortical inhibition after both sham injury ($p=0.002$) and TBI ($p=0.02$). There was a trend in lower magnitude of HupA-induced cortical inhibition in TBI animals than in sham-TBI animals. However, time to maximal HupA effect was delayed in the TBI group. The median time to maximum HupA inhibition in sham and TBI groups were 46.4 and 76.5 minutes, respectively ($p=0.03$). This is consistent with a quadratic trend comparison

that projects HupA-mediated cortical inhibition to last longer in injured rats (p=0.007). **Conclusions:** We show that (1) cortical GABA-mediated inhibition, as measured by ppTMS, decreases acutely after TBI, and (2) HupA restores lost post-TBI GABA-mediated inhibition, and (3) HupA-mediated enhancement of cortical inhibition is delayed after TBI. We anticipate that these and analogous experiments will enable improved dosing of neuropsychiatric medications after brain injury.

Disclosures: U. Damar: None. **R. Gersner:** None. **J. Johnstone:** A. Employment/Salary (full or part-time):; Biscayne Neurotherapeutics Inc.. **K. Kapur:** None. **S. Collins:** A. Employment/Salary (full or part-time):; Biscayne Neurotherapeutics Inc. **S.C. Schachter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biscayne Neurotherapeutics Inc.. F. Consulting Fees (e.g., advisory boards); Biscayne Neurotherapeutics Inc. **A. Rotenberg:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Biscayne Neurotherapeutics.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.11/N3

Topic: B.11. Epilepsy

Title: Investigation of the effect of licofelon on absence epilepsy

Authors: *T. SAHIN, F. DEDE, N. ATES
Physiol. Dept., Kocaeli Univ. Med. Fac., Kocaeli, Turkey

Abstract: Usually beginning in childhood, absence epilepsy is one type of non-convulsive epilepsies. Recent studies have suggested that some specific inflammatory pathways may be related with the pathogenesis of epilepsy. Cyclooxygenase (COX) and lipoxygenase (LOX) are key enzymes involved in the arachidonic acid cascade, lead to the release of pro-inflammatory mediators. Licofelone is an anti inflammatory agent, reduces inflammation by blocking the COX and LOX pathway. The aim of this study is to demonstrate the possible anti-epileptic effects of licofelone on spike-wave discharges (SWDs) occurance in the absence epileptic Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats strain. Twelve male six months old WAG/Rij rats, born and raised in the laboratory of Kocaeli University, served as subjects in our study. Three groups were created as, 10 mg/ kg/ ip licofelone (n=4) , DMSO control (n=4) and salin control (n=4). All rats were implanted with tripolar electrode sets which were placed on the frontal cortex, parietal cortex and cerebellum. The short and long term effects of licofelone administration were investigated on electroencephalography (EEG) recordings in basal conditions (one hour before the injections were done) and at 1. , 2. and 24. hours. DMSO administration did not cause any

differentiation in the number and total duration of SWD at 24.hour compared to the baseline and first hour. On the other hand licofelone administration reduced the number and total duration of SWD at 24. hour, compared to the both. According to our results; the long term effect of licofelon is reduction in the number and total duration of SWD in absence epilepsy. Licofelone may have anti-epileptic effects in absence epileptic WAG/Rij rats. Experiments of this study are currently in progress.

Disclosures: T. Sahin: None. **F. Dede:** None. **N. Ates:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.12/N4

Topic: B.11. Epilepsy

Title: Resampling technique effects for lasso in seizure prediction

Authors: *P.-N. YU[1], *P.-N. YU[2], C. N. HECK[1], C. LIU[1], D. SONG[2], T. W. BERGER[2]
[2]Biomed. Engin., [1]USC, Los Angeles, CA

Abstract: Patients with epilepsy suffer from unexpected and uncontrolled seizures and may be vulnerable in dangerous situations, such as standing on a staircase or swimming. To avoid such situations and enable patients to move to a safer place, it would be clinically useful to have a device to warn a patient an upcoming seizure. Seizure prediction using power spectrum, cross-correlation coefficients and autoregressive model coefficients as features along with lasso classifier scored around 0.8 areas under the classification curve (AUC), much better than random guessing having an AUC around 0.5. That score, however, cannot be an informative index to warn patients the upcoming seizures. A practical way for patients is a binary index which simply lets a patient know whether a seizure is coming or not. For binary classification, a common problem need to be resolved is that a predictor would give a predictive probability toward to the majority class as opposed to the minority class when the majority class (i.e. interictal data) outnumbers the minority class (i.e. preictal data). To counteract the problem of imbalanced data, this study proposes using resampling techniques to change the class distribution and make the data balanced. Random undersampling, random oversampling and SMOTE (synthetic minority oversampling technique) were used to resample features generated from the power spectrum, cross-correlation coefficients and autoregressive model coefficients and then lasso predictor was used to classify those features into interictal samples and preictal samples. The higher area under classification curve and Matthews correlation coefficients in 4 subjects with 53 sets of seizures suggest that SMOTE is the most appropriate resampling technique.

Disclosures: **P. Yu:** None. **P. Yu:** None. **C.N. Heck:** None. **C. Liu:** None. **D. Song:** None. **T.W. Berger:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.13/N5

Topic: B.11. Epilepsy

Support: SIP-IPN Grant 20171716

Title: Benzenamides as anticonvulsants

Authors: *S. E. MEZA TOLEDO, C. MARTÍNEZ APARICIO, E. FUENTES CAPISTRÁN, E. ROMERO MARTÍNEZ
Dept. de Bioquímica, Escuela Nacional De Ciencias Biológicas, IPN, Ciudad de Mexico, Mexico

Abstract: In an effort to discover novel anticonvulsants, we prepared and characterized several benzenamides and studied their anticonvulsant activity against seizures induced by convulsants drugs acting at the gamma-aminobutyric acid (GABA) neurotransmission, in CD-1 mice. Compounds 2-hydroxy-2-ethyl-2-phenyl butyramide (1), 2-hydroxy-2-(3'-trifluoromethylphenyl)butyramide (2), 2-hydroxy-2-(3',5'-bis(trifluoro methylphenyl) butyramide (3), 3-hydroxy-3-ethyl-3-phenyl pentanamide (4), 3-hydroxy-3-(3'-trifluoromethylphenyl) pentanamide (5) and 2-hydroxy-2-(3',5'-bis(trifluoromethylphenyl) pentanamide (6) were prepared using condensation reactions and characterized through infrared spectrophotometry and nuclear magnetic resonance spectroscopy. Each of the six compounds exhibited a significant anticonvulsant activity in mice against seizures induced by bicuculline, a competitive $GABA_A$ receptor antagonist, or thiosemicarbazide, a glutamate decarboxylase inhibitor, the enzyme which produces GABA. Incorporation of trifluoromethyl groups in the phenyl ring of compounds 2, 3, 5 and 6 increased their anticonvulsant activity respect non-halogenated compounds 1 and 4. The protection by benzenamides against seizures induced by convulsant drugs which block GABA neurotransmission suggests that they may be acting through GABAergic mechanisms. This study shows that benzenamides represent a new class of anticonvulsant compounds worthy of further development for potential antiepileptic therapy.

Disclosures: **S.E. Meza Toledo:** None. **C. Martínez Aparicio:** None. **E. Fuentes Capistrán:** None. **E. Romero Martínez:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.14/N6

Topic: B.11. Epilepsy

Title: Suppression of epileptic activity by lactate in subicular pyramidal neurons

Authors: *P. JORWAL, S. K. SIKDAR
Mol. Biophysics Unit, Indian Institue of Sci., Bangalore, India

Abstract: Epilepsy is a group of neurological disorders characterized by unprovoked recurrent seizures. Many evidences suggest that the subiculum in hippocampus plays an important role in initiation and maintenance of epileptic discharges. Lactate is neuroprotective against various types of brain damage including ischemic, excitotoxic, and mechanical insults. Increased cerebral metabolic activity during epileptic discharges is accompanied by excess brain lactate formation which reaches upto 5-6 mM during seizures. We investigated the effect of lactate on subicular pyramidal neurons after induction of epileptogenesis using 4AP-0Mg^{2+} in an in vitro epilepsy model in rats. We found that application of 6 mM lactate after epileptic induction reduced spike frequency and hyperpolarised the resting membrane potential of subicular pyramidal neurons in whole cell patch clamp experiments in acute hippocampal slices. G Protien-coupled receptor 81 (GPR81) is present in many regions of brain and it gets activated with 6 mM lactate, so we hypothesized that the effect of lactate might be through GPR81 receptors. Therefore the expression of GPR81 was checked using immunohistochemistry and it was found to be present in subicular pyramidal neurons. To study the signaling mechanism involved behind the effect of lactate, a specific GPR81 agonist- 3,5-dihydroxybenzoate and antagonist- 3-hydroxy-butyrate was used. Electrophysiological recordings showed reduction in spike frequency and hyperpolarization in the presence of agonist but not in presence of GPR81 antagonist. Our findings suggest a new role of lactate as a neuroprotectant acting via GPR81 receptor in subicular pyramidal neurons.

Disclosures: P. Jorwal: None. **S.K. Sikdar:** A. Employment/Salary (full or part-time):; Ministry of human resource and development,Goverment of India. 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.; Ministry of human resource and development. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Department of biotechnology, Ministry of human resource and development.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.15/N7

Topic: B.11. Epilepsy

Title: Evaluating the anti-inflammatory effects of curcumin in Scn1a mouse models of epilepsy

Authors: *A. B. VAN DERVEER[1], S. B. DUTTON[2]
[1]Neurosci., Agnes Scott Col., Colorado Springs, CO; [2]Biology/ Neurosci. Program, Agnes Scott Col., Decatur, GA

Abstract: Epilepsy is characterized by recurrent seizures that are not provoked. There are various forms of epilepsy, varying in seizure severity and age of occurrence. Of particular interest are the epilepsy syndromes Genetic Epilepsy with Febrile Seizures Plus (GEFS+) and Dravet Syndrome (DS). Both syndromes are caused by mutations in the voltage gated sodium channel $Nav_{1.1}$ (gene *SCN1A*). Patients with these epilepsy syndromes experience severe febrile and afebrile seizures and are often refractory to current available pharmacological treatments. Therefore, there exist a need for the development of alternative treatment options to alleviate the frequency and/or occurrence of seizures in this patient population. Curcumin, the primary constituent of turmeric, has been shown to reduce cell death and decrease inflammation in experimental models of epilepsy. To determine if curcumin would be an effect treatment for patients with *SCN1A* mutations, we first determined the neuroprotective properties of curcumin in Pc12 cells using the glutamate toxicity paradigm. We then evaluated the ability of curcumin to alter the expression of the proinflammatory cytokines IL-6, IL-Iβ, and TNF-α in a mouse model of *Scn1a* epilepsy. Our results indicate alterations in expression and suggest the potential usages of curcumin in this patient population.

Disclosures: A.B. Van Derveer: None. **S.B. Dutton:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: B.11. Epilepsy

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The authors are grateful to the Department of Science and technology, New Delhi, India to provide funding (Grant no: INT/RUS/RFBR/P-244/2016).

Title: Ferulic acid supplementation for management of depression in epilepsy

Authors: *T. SINGH, R. K. GOEL
Dept. Of Pharmaceut. Sci. and Drug Res., Punjabi University, Patiala, Patiala, India

Abstract: Neuroinflammation driven altered neurochemical milieu have been reported to play a significant role in pathogenesis of comorbid depression in epilepsy. Most of the antiseizure drugs (ASDs) such as levetiracetam, taigabine, topiramate have not been reported any significant effect in alleviating neuroinflammation, which may explain their ineffectiveness in ameliorating depression associated with epilepsy. The supplementation of antidepressants (ADs) attracts various pharmacokinetic and pharmacodynamic interactions with ASDs and was considered unsafe in epilepsy. This scenario pushes us to search therapies beyond ADs by critically exploring the disease mechanism. Thus, as suggested by our previous findings, anti-inflammatory phytotherapy (Ferulic acid) appears a promising adjuvant therapy with levetiracetam for effective and safe management of depression associated with epilepsy. Pentylenetetrazole kindling induced epileptic animals were treated with vehicle, levetiracetam (40mg/kg/day i.p.) and levetiracetam in combination with two doses of ferulic acid (40mg/kg; 80mg/kg)/day/p.o. for 15 days. Every 5^{th} day during the treatment, depression was evaluated and animals were administered pentylenetetrazole to evaluate the effect of different pharmacological interventions on seizure severity. The epileptic animals were reported decreased seizure threshold associated with comorbid depression. The treatment with levetiracetam was found ineffective in ameliorating the associated depression, however ferulic acid supplementation with levetiracetam ameliorated comorbid depression supported by restoration of elevated circulating corticosterone levels as well as proinflammatory cytokines (IL-1β, TNF-α) and indoleamine 2,3-dioxygenase activity in mice brain. Thus, suggesting supplementation of anti-inflammatory phytomolecules such as ferulic acid as safe and effective adjuvant therapy for the management of comorbid depression in epilepsy.

Disclosures: **T. Singh:** A. Employment/Salary (full or part-time):; Indian Council of Medical Research, New Delhi, India. Project no. BIC/11(02)/2015. 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.; Department of Science and technology, New Delhi, India to provide funding (Grant no: INT/RUS/RFBR/P-244/2016). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Department of Science and technology, New Delhi, India to provide funding (Grant no: INT/RUS/RFBR/P-244/2016). **R.K. Goel:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.17/N9

Topic: B.11. Epilepsy

Title: Analysis of the anticonvulsant properties of thalidomide in mice

Authors: *A. M. ISLAS, C. CAMPOS-RODRÍGUEZ, A. ALVAREZ-GUERRA, E. RAMÍREZ-SAN JUAN
Physiol., Escuela Nacional De Ciencias Biológicas, Inst., Ciudad de México, Mexico

Abstract: Thalidomide was introduced in the 1950s as an antiepileptic drug. In 1957, it was commercialized as a safe sedative and it was widely used as an antiemetic. However, in 1961, it was withdrawn from the market because of its teratogenic effects. After thalidomide's output of the market, other outstanding pharmacological properties were discovered. Despite all of its therapeutic applications, none of them was used for the treatment of primary neurologic or psychiatric diseases, main reason why it was synthesized. Although there is history of the anticonvulsant effects of thalidomide in rats and antiepileptic effects in patients, there is no evidence of a systematic study of its anticonvulsant properties in mice, so in this protocol, we analyzed the possible protective effects of thalidomide against pentylenetetrazol (PTZ) and 4-aminopyridine (4-AP)-induced seizures, essential models in the studies of potential antiepileptic agents. Male CD1 mice were distributed randomly in 5 groups of 12 animals each one. The treatments for the groups were: carboxymethylcellulose 0.5% in phosphate buffer solution, sodium valproate dose of 300 mg/kg for PTZ model and dose of 400 mg/kg for 4-AP model, and thalidomide in three different doses (100, 200 and 400 mg/kg), all of the treatments were injected intraperitoneally. After 1 hour of the treatment with thalidomide (30 minutes for groups treated with sodium valproate), we administered subcutaneously the convulsant agents PTZ (90 mg/kg) or 4-AP (10 mg/kg) respectively and we evaluated variables such as latency and number of seizures, duration of seizures, percentage of animals convulsed and dead, and the latency of the death. In addition, a locomotor activity test was performed to prove the sedative effect of thalidomide, we used 4 groups of 12 mice each one, with a control group and 3 groups treated with the thalidomide's proved doses. The results show that thalidomide reduces significantly the locomotor activity starting from 100 mg/kg, due to significant decreases found on the ambulation and stereotypy time in mice treated with thalidomide, as well as a significant increase in the immobility time. Otherwise, the 4-AP model does not show a significant decrease in the percentage of convulsed and dead animals treated with thalidomide comparing with the control group. While the PTZ model shows favorable significant differences on the variables mentioned above in the groups treated with thalidomide compared with the control group. We found that

thalidomide (1) induces the typical sedative effects, (2) has not anticonvulsant effect in mice treated with 4-AP and (3) has anticonvulsant effect, dose dependent, in mice treated with PTZ.

Disclosures: A.M. Islas: None. **C. Campos-Rodríguez:** None. **A. Alvarez-Guerra:** None. **E. Ramírez-San Juan:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: B.11. Epilepsy

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MRC PhD Studentship 1272510

Department of Neurology, Chang Gung Memorial Hospital Linkou Medical Center and Chang Gung University College of Medicine, Taoyuan, Taiwan – Scholarship CMRPG3C1021-1025

Title: Gene therapy for epilepsy using non-integrating lentiviral delivery of an engineered potassium channel gene

Authors: *A. SNOWBALL, E. CHABROL, B.-L. CHANG, A. LIEB, M. C. WALKER, D. M. KULLMANN, S. SCHORGE
UCL Inst. of Neurol., London, United Kingdom

Abstract: Gene therapy is a promising treatment strategy for pharmacoresistant epilepsy. While several approaches have demonstrated preclinical efficacy, their suitability for clinical translation can be brought into question by poor vector or study design. Here we present a novel gene therapy vector designed and tested to maximize its translational potential. The vector encodes a Kv1.1 voltage-gated potassium channel gene, *KCNA1*, engineered to increase channel expression and reduce inactivation. To improve safety, the engineered *KCNA1* sequence is placed under a CAMK2A promoter to restrict transgene expression to excitatory neurons, and packaged into an integration-deficient lentivirus to reduce the risk of insertional mutagenesis. When injected into the rat visual cortex, our lentivector was well tolerated and drove transgene expression specifically within the target excitatory neuron population. In a randomized, blinded, preclinical trial, our treatment rapidly and persistently suppressed seizures in a rodent model of focal

neocortical epilepsy. This demonstration of therapeutic efficacy in a clinically-relevant setting, combined with the improved safety conferred by cell type specific expression and integration-deficient delivery, suggest our optimized gene therapy is well placed for clinical translation in the treatment of refractory focal epilepsy.

Disclosures: **A. Snowball:** None. **E. Chabrol:** None. **B. Chang:** None. **A. Lieb:** None. **M.C. Walker:** None. **D.M. Kullmann:** None. **S. Schorge:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.19/N11

Topic: B.11. Epilepsy

Support: NIH CounterACT Center grant 1U54NSO79202

Title: Intramuscular midazolam, allopregnanolone and perampanel combination therapy terminates seizures in a rat model of DFP-induced status epilepticus

Authors: *A. DHIR, M. A. ROGAWSKI
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Abstract: Status epilepticus (SE), a common neurological complication of organophosphate (OP) poisoning, is associated with brain damage and ultimately death. The first line therapies of choice are benzodiazepines, especially diazepam or midazolam. These drugs have reduced efficacy or are ineffective when administered following a delay after the onset of seizures. Allopregnanolone, a neurosteroid agent that acts on both synaptic and extrasynaptic GABA-A receptors, potentiates the effect of benzodiazepines on GABA-A receptors. Excessive cholinergic stimulation in OP poisoning leads rapidly to glutamate release, which plays a critical role in the seizure activity through an action on excitatory ionotropic glutamate receptors, including AMPA receptors. The present study evaluated the effect of addition of allopregnanolone and the AMPA receptor antagonist perampanel to standard therapy with midazolam in a DFP (diisopropylfluorophosphate) SE animal model. SE was induced in male Sprague-Dawley rats with a 4 mg/kg, SC injection of DFP, followed 1-min later by intramuscular administration of atropine (2 mg/kg, IM) and pralidoxime (25 mg/kg, IM). The triple therapy was administered 40 min after DFP administration. Animals were continuously monitored for a minimum of 5 h using video-EEG from cortically implanted electrodes. Behavioral seizures were scored using a modified Racine scale. DFP induced robust continuous behavioral and EEG seizures within minutes of its administration and was associated with high mortality. Midazolam (1.8 mg/kg, IM) was ineffective in terminating SE in these rats. Dual therapy with midazolam and allopregnanolone (6 mg/kg, IM) caused a reduction in the seizure score and cessation of

electrographic SE in 83% of the animals; the remaining animals continued to exhibit electrographic seizures and spikes. Triple therapy with midazolam, allopregnanolone and perampanel (2 mg/kg, IM) stopped both behavioral and electrographic SE within a few minutes of administration in 100% of the animals tested. There was no mortality in any of the treatment groups. Both dual and triple therapy resulted in sedation. In conclusion, addition of allopregnanolone or allopregnanolone plus perampanel to standard-of-care benzodiazepine therapy caused rapid seizure termination, and may represent promising approaches to manage OP nerve agent-induced SE.

Disclosures: A. Dhir: None. **M.A. Rogawski:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UC Davis.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.20/N12

Topic: B.11. Epilepsy

Support: NIH Grant R44 NS086343 to X.Xie

NIH Grant 43DE026094 to X.Xie

NIH Grant R44 AG043203 to X. Xie

NIH Grant MH074427 to C.D. Weaver

Title: GIRK activator ML297 depresses epileptiform afterdischarges and seizure propagation in mouse brain slices using conventional and MEA extracellular recordings

Authors: *B. ZOU[1], W. CAO[1], C. PASCUAL[1], K. XIAO[1], C. LINDSLEY[2], D. WEAVER[2], X. XIE[1]
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Abstract: G protein-gated inwardly-rectifying potassium (GIRK) channels have been implicated in various pathophysiological conditions in the nervous system including epilepsy, addiction, ataxia and Parkinson’s disease. Although this important channel has been intensively studied, a selective and potent activator was not available until the recent discovery of the GIRK biologic probe ML297, a selective direct activator of the GIRK channel. Field potential with a population of spikes were recorded extracellularly using a single glass pipette or multi channels array (MEA) in hippocampal or thalamus brain slices prepared from either young or old mice. In general, brain slices from aged animals were prone to generate epileptiform afterdischarges

following the initial population of spikes. Perfusion of low Ca^{2+} (0.2mM), 0 Mg^{2+} or the voltage-gated potassium channel blocker, 4-Aminopyridine (4-AP, 3 - 50µM), induced afterdischarges in slices from young animals and exacerbated seizure activity in slices from aged animals. All afterdischarges induced by these three conditions were completely blocked by ML297 (10 - 30 µM). A low dose of 4-AP (3 µM) induced multiple afterdischarges resembling those induced by low Ca^{2+} or 0 Mg^{2+}. A high dose of 4-AP (50 µM) induced more afterdischarges and also caused elevation of baseline, suggesting hyperpolarization. ML297 (10 - 30 µM) completely blocked low-dose 4-AP induced-afterdischarges without affecting the elevated baseline. Low Ca^{2+} (0.2mM) or 0 Mg^{2+} induced seizure activity propagating multiple sites in the slices containing the hippocampus and thalamus revealed by MEA recording. The seizure propagation was blocked with ML297 (10 - 30 µM). These results indicate that direct activation of GIRK powerfully depresses neuronal excitability and prevents synchronized firing in multiple recording sites. Direct GIRK activation is a potential new approach to treat partial and generalized seizures involved in the whole brain. **Key words:** 4-Aminopyridine, Epilepsy, GIRK, hippocampus, MEA, seizure

Disclosures: B. Zou: None. **W. Cao:** None. **C. Pascual:** None. **K. Xiao:** None. **C. Lindsley:** None. **D. Weaver:** None. **X. Xie:** 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.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

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Program#/Poster#: 665.21/O1

Topic: B.11. Epilepsy

Support: EU Grant 602102 EPITARGET

Studienstiftung des deutschen Volkes

Title: Alterations of the cholinergic system during epileptogenesis in animal models of temporal lobe epilepsy

Authors: S. MELLER[1], C. BRANDT[1], J. KLEIN[2], *W. LOSCHER[1]
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Abstract: Purpose: Epileptogenesis is often induced by brain insults so that patients at risk for epilepsy can be identified. Therefore, a prophylactic pharmacological intervention after the initial brain insult may be possible, but as yet this is an unmet clinical need. Based on recent data

on a potential role of the cholinergic system in epileptogenesis, pharmacological modulation of this system in the brain might provide a new approach to interfere with epileptogenesis. For instance, high extracellular levels of the excitatory neurotransmitter acetylcholine (ACh) seem to play an important role in initiation and maintenance of status epilepticus (SE) in the pilocarpine rat model of acquired epilepsy. However, its role as a putative pro-epileptogenic factor is not well understood and, therefore, is investigated in the present study.
Method: Extracellular alterations of hippocampal ACh concentrations were assessed during SE and post-SE epileptogenesis. For this purpose, two post-SE models of temporal lobe epilepsy were used in female Sprague Dawley rats: the pilocarpine model and a model with SE induction by prolonged electrical stimulation of the basolateral amygdala (BLA model). In both models the SE acts as the initial brain insult. We used microdialysis to sample extracellular fluid in the hippocampus before induction of SE (baseline), while SE was developing, and after termination of SE by diazepam and phenobarbital. In addition, we collected samples during epileptogenesis at day 1, 4, 8, and during the chronic phase 10 weeks after SE. Animals were video-EEG monitored for one week during both the latency and the chronic phase. ACh concentration was measured by high-performance liquid chromatography.
Results: First data show that levels of hippocampal ACh in rats increase rapidly during development of SE and decrease immediately below baseline values after termination of SE in both models. Concentrations of ACh during epileptogenesis, however, only show slight alterations in comparison to sham controls.
Conclusions: Our measurements do not reveal alterations in extracellular concentrations of ACh during epileptogenesis neither in the pilocarpine model nor in the BLA model. Latter was used to investigate a non-cholinergic stimulus of SE induction. However, alterations of cholinergic receptors during epileptogenesis cannot be excluded. This issue will be addressed by antiepileptogenesis studies with the muscarinic antagonist scopolamine.

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Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

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Topic: B.11. Epilepsy

Support: NIH Grant 5R01NS034700-22

Title: Protracted post-traumatic neuronal death in the developing hippocampus

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Abstract: New fluorophores and microscopy techniques have made possible more detailed explorations of the process of neuronal death. In the present study we evaluated the death of neurons in a chronically epileptic in vitro preparation in which multiphoton microscopy could be performed over a period of several days. Organotypic hippocampal slice cultures were made from wild-type C57BL/6J mice, and imaged with transgenic fluorophores as well as the Na^+ dye SBFI. Organotypic slice cultures were prepared on P6 and incubated *in vitro* until use, with SBFI added 24 hours prior to imaging. Two-photon imaging was used to excite SBFI at both Na^+-sensitive and -insensitive wavelengths, allowing for the ratiometric determination of the $[Na^+]_i$. Immediately post-trauma, neurons had significantly higher $[Na^+]_i$ than has been reported in undamaged neurons. After a brief recovery period, $[Na^+]_i$ again rose to high levels and remained elevated for days. Elevated $[Na^+]_i$ followed decreased synthesis of virus-induced fluorescent proteins such as TurboRFP and genetically-encoded fluorescent indicators such as Clomeleon, preceded morphological changes such as cell shrinkage and retraction of processes, and coincided with increases in membrane permeability (allowing for the passive influx of dyes and stains such as propidium iodide) and elevated caspase activity (as indicated by FLICA positivity). The high $[Na^+]_i$ was mitigated by the activity of Na^+/K^+ ATPases, cation/Cl^- cotransporters, and Na^+/Ca^{2+} exchangers in order to support high rates of transmembrane Na^+ flux during epileptogenesis. Inhibition of COX-2 and the protein Bax significantly lowered $[Na^+]_i$, and antibody staining demonstrated that the Bax-inhibiting peptide V5 caused a reduction in the number of cells expressing Bax, with a homozygous Bax knockout mouse showing almost no expression. This suggests that an apoptotic pathway leading to an increase in cytoplasmic membrane permeability may be responsible for the rise in $[Na^+]_i$ and related changes. Overall, a stereotypical sequence of events preceded neuronal death by at least several days, and often over a week. This began with quenched emission of fluorescent proteins, and continued with dendritic retraction, elevation in $[Na^+]_i$, and terminal cell shrinkage. ATPase activity and secondary ion transport remained robust throughout this process. We are currently investigating the role of mitochondria in producing ATP in these neurons, as well as testing whether the mitigation of elevated $[Na^+]_i$ reflects a translationally useful neuroprotective effect or a specific effect on $[Na^+]_i$.

Disclosures: **T. Balena:** None. **Y. Saponjian:** None. **K.J. Staley:** None.

Poster

665. Epilepsy: Anticonvulsant Therapies - Novel Screens, Drugs, and Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 665.23/O3

Topic: B.11. Epilepsy

Support: Epilepsy Foundation, project number EF 14-08

Title: Effects of inhibition of the mammalian target of rapamycin (mTOR) pathway in an organotypic slice culture model for temporal lobe epilepsy: Anti-epileptogenic properties of curcumin

Authors: *C. M. DRION[1], L. KOOIJMAN[1], E. ARONICA[2,1,3], E. A. VAN VLIET[2], W. J. WADMAN[1], P. CHAMEAU[1], J. A. GORTER[1]
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Abstract: Inhibition of the mammalian target of rapamycin (mTOR) pathway could be anti-epileptogenic in temporal lobe epilepsy (TLE), possibly via anti-inflammatory actions. We studied effects of rapamycin and curcumin, both mTOR inhibitors with anti-inflammatory properties, on epileptogenesis and inflammation in an in vitro rodent model of TLE: the organotypic slice culture. Slice cultures containing hippocampus and parahippocampal cortex were made from 6-day-old rat pups and maintained in culture for up to 3 weeks. Rapamycin (20 nM), curcumin (10 µM) or vehicle (0.05% DMSO) was added to the culture medium from day 2 in vitro onwards. Western blot analysis indicated that mTOR activation (shown as the phosphorylated-S6/S6 ratio) was suppressed after 1, 2 and 3 weeks by both rapamycin and curcumin. Whole cell patch-clamp recordings and field potential recordings were performed in the *cornu ammonis* (CA) 1 of cultures at 1, 2 and 3 weeks in vitro, without the drugs present in the recording medium (artificial cerebrospinal fluid). Immunohistochemistry was used to study the development of slice architecture and qPCR was used to study expression of inflammatory markers. Electrophysiological recordings revealed epileptic-like activity that developed over 3 weeks in vitro. In week 3, seizure-like events (SLE) could be detected in whole cell recordings from CA1 principal neurons. Field potential recordings revealed that these SLE were also present at the network level. The percentage of recorded CA1 neurons displaying SLE was 72.5% (29/40) in vehicle-treated slices, 52% (13/25) in rapamycin-treated slices ($p = 0.11$ compared to vehicle), and 25.8% (8/31) in curcumin-treated slices ($p < 0.01$ compared to vehicle). Preliminary qPCR results show lower values of inflammatory markers interleukin 1β (IL-1β), interleukin 6 (IL-6) and transforming growth factor β (TGF-β) after 3 weeks of treatment with both rapamycin and curcumin compared to vehicle, although the data did not reach significance. Our results show that curcumin can suppress SLEs in an organotypic slice culture model for TLE, suggesting anti-epileptogenic properties of curcumin in vitro that may be related to anti-inflammatory actions.

Disclosures: C.M. Drion: None. **L. Kooijman:** None. **E. Aronica:** None. **E.A. van Vliet:** None. **W.J. Wadman:** None. **P. Chameau:** None. **J.A. Gorter:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.01/O4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R15 AG046915

Title: Abeta oligomers: Biophysical properties predict cellular pathogenesis

Authors: *M. A. MOSS[1,2], K. M. PATE[1], D. N. DEAN[3], V. RANGACHARI[3]
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Abstract: Alzheimer's disease (AD), the leading cause of dementia in the elderly, is characterized by the presence of amyloid plaques in the brain parenchyma and cerebrovasculature. These deposits are comprised primarily of aggregated amyloid-β protein (Aβ). In particular, Aβ oligomers have emerged as the primary toxic agents responsible for early synaptic dysfunction and neuronal death. Despite observations that Aβ oligomers elicit a number of physiological responses, ranging from alterations in protein expression to cell death, the identity of the oligomer specie(s) accountable for these responses remains uncertain. Thus, it is important to characterize the physiological activity elicited by different Aβ oligomer species. To explore this relationship, we have paired biophysical characterization techniques for Aβ oligomers with a cell culture system that probes oligomer physiological acidity.
SH-SY5Y human neuroblastoma cells were used evaluate the manner in which large fatty acid derived oligomers (LFAOs) can influence Aβ-induced neuronal death, and results revealed an unexpected inverse dose-response. In contrast, activation of a broad spectrum of caspases correlated directly with concentration, suggesting distinct mechanisms for these two cellular responses. These observed differences in physiological activity were found to correspond to changes in oligomer biophysical properties associated with their self-propagative nature. Specifically, a concentration-dependent shift in LFAO size from a 12-mer to a 24-mer and the associated changes in surface hydrophobicity may alter the manner in which oligomers to interact with neuronal cells. This work reveals an important interplay between the biophysical characteristics of Aβ oligomers and their physiological activity. Further knowledge of these relationships has the potential to direct therapeutic strategies aimed at modulating Aβ oligomer formation.

Disclosures: **M.A. Moss:** None. **K.M. Pate:** None. **D.N. Dean:** None. **V. Rangachari:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.02/O5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AG054025

NS094557

Title: Generation and characterization of neurotoxic tau oligomers

Authors: *G. GHAG, D. V. CANTU, M. J. GUERRERO-MUNOZ, U. SENGUPTA, R. KAYED
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Abstract: Various studies have proposed that fibrillary aggregates of tau and other amyloidogenic proteins are neurotoxic and result in numerous neurodegenerative diseases. However, these studies usually involve sonication or extrusion through needles prior to the experimentation. As a consequence, these methods may fragment large aggregates in the sample, producing a mixture of aggregated species rather than intact fibrils; therefore, the results of these experiments may be reflective of other amyloidogenic species, such as oligomers and/or protofibrils. In order to investigate the effects of sonication on the aggregation of tau and other amyloidogenic proteins, fibrils were prepared and well-characterized, then sonicated and evaluated by various biochemical and biophysical methods to identify the aggregated species present. We found that indeed a mixture of aggregated species was present along with the fibrils indicating that sonication leads to impure fibril samples and should be analyzed with caution. Our results corroborate the previous studies showing that sonication of prion and Aβ fibrils leads to the formation of toxic, soluble aggregates. We also show that the oligomeric forms are the most toxic species, though it is unclear precisely how sonication causes oligomer formation. Results from our lab suggest that these small toxic oligomers produced by sonication, rather than the stable fibrillar structures, are prion-like in nature, acting as seeds to induce the misfolding of tau and other amyloidogenic proteins.

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Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.03/O6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH

Title: Molecular insights into Aβ oligomer strains and phenotypic variations in AD

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[1]Chem. and Biochem., Univ. of Southern Missisippi, Hattiesburg, MS; [2]Chem. and Biochem., Univ. of Southern Mississippi, Hattiesburg, MS

Abstract: Widespread phenotypic differences observed among Alzheimer disease (AD) patients are one of the diverse clinical manifestations in all neurodegenerative diseases. Deciphering the molecular mechanisms that underpin such differences especially for an idiopathic disease is rather challenging. Aggregation of amyloid-β (Aβ) peptides has long been known as the key trigger in AD pathology. Polymorphism observed within the aggregation end products of Aβ fibrils seem to correlate with clinically observed pathologic variations, which has in part, corroborated the hypothesis that ‘conformeric strains’ of Aβ aggregates could manifest in distinct phenotypic outcomes. In our lab, we propose to understand this phenomenon in the context of whether and how the strains of low molecular weight oligomers could propagate their structure faithfully towards morphologically distinct fibrils with conspicuous pathological phenotypes. By biophysical investigations, we recently demonstrated that an Aβ42 dodecamer called Large Fatty Acid derived Oligomers (LFAOs) is able to quantitatively replicate at low concentrations, and at elevated concentrations, propagate their mesoscopic structure faithfully towards morphologically unique fibrils containing the discrete LFAO units. Furthermore, LFAO-seeded aggregates were able to selectively induce massive amounts of cerebral amyloid angiopathy (CAA) to transgenic CRND8 mice as opposed to unseeded or fibril seeded aggregates, which induced more parenchymal deposits. Results based on our model oligomer demonstrate that certain oligomeric strains could faithfully propagate their structure towards distinct fibrils and induce selective pathological phenotypes in the brain. Overall, these results bring forth important mechanistic insights into strain specific propagation of oligomers that have remained elusive thus far.

Disclosures: V. Rangachari: None. **D.N. Dean:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.04/O7

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: HDAC6 inhibitor tubastatin A reduces pathological tau burden in the brain of transgenic AD mice model

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Abstract: A large portion of dementia patients are suffering from Alzheimer’s disease (AD). AD has two typical pathological phenotypes, neurofibrillar tangle (NFT) and amyloid beta (Aβ) plaques. NFTs are composed of tau protein aggregates. Tau undergoes diverse post translational modifications (PTMs) such as phosphorylation, ubiquitination, glycosylation and acetylation. PTMs are considered as important features of abnormal pathological tau. This study focused on acetylation by inhibiting HDAC6 (histone deacetylase 6) in AD pathology because acetylated tau contributed for AD pathogenesis. Axonal transport deficit caused by Aβ was recovered by up-regulating acetylation level by tubastatin A (TBA), HDAC6 inhibitor, in primary hippocampal neuron culture. Acetylation level was increased by intraperitoneal injection of TBA on AD mice model, resulting in significant recovery of memory deficits. TBA also reduced phosphorylated tau in sarkosyl-insoluble fraction and AT 180 immuno-reactive tau, but did not altered Aβ pathology and gliosis in these mice. With these data, we suggest targeting HDAC6 inhibition is a good therapeutic target by reduction of tau burden in AD.

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Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF (2015R1A2A1A05001794, 2014M3C-7A1046047, MRC (2011-0030738))

NRF (2014M3C7A1046042)

NRF (2015R1C1A2A01053545)

Title: Chemically treated plasma Aβ is a potential blood-based biomarker for screening cerebral amyloid deposition

Authors: *J. PARK[1], S.-H. HAN[1], H. CHO[1], M. BYUN[2], D. YI[2], Y. CHOE[3], S. KANG[1], E. JUNG[1], S. WON[1], E. KIM[1], Y. KIM[4], D. LEE[2], I. MOOK-JUNG[1]
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Abstract: Plasma β-Amyloid (Aβ) is a potential candidate for an Alzheimer's disease (AD) biomarker because blood is an easily accessible bio-fluid, which can be routinely collected, and Aβ is one of the major hallmarks of AD pathogenesis in the brain. However, the association between plasma Aβ levels and AD diagnosis is still unclear due to the instability and inaccurate measurements of plasma Aβ levels in the blood of patients with AD. If a consistent value of plasma Aβ from the blood can be obtained, it might provide a clue whether plasma Aβ is a potential biomarker for AD diagnosis. We predicted the brain amyloid deposit by measuring the plasma Aβ levels. This cross-sectional study included 353 participants (215 cognitively normal, 79 with mild cognitive impairment, and 59 with AD dementia) who underwent Pittsburgh-compound B Positron Emission Tomography (PiB-PET) scans. We treated a mixture of protease inhibitors and phosphatase inhibitors (MPP) and detected plasma Aβ42 and Aβ40 (MPP-Aβ42 and MPP-Aβ40) in a stable manner using xMAP technology. MPP-Aβ40 and MPP-Aβ42/40 (MPP-Aβs) were significantly different between subjects with positive amyloid deposition (PiB+) and those with negative amyloid deposition (PiB-) (***$P < 0.0001$). Furthermore, MPP-Aβ40 (***$P < 0.0001$, $r = 0.23$) and MPP-Aβ42/40 (***$P < 0.0001$, $r = -0.23$) showed significant correlation with global PiB deposition (SUVR) respectively. In addition, our integrated multi-variable (MPP-Aβ42/40, gender, age, and Apolipoprotein E genotypes) logistic regression model proposes a new standard for the prediction of cerebral amyloid deposition. MPP-Aβ might be one of the potential blood biomarkers for the prediction of PiB-PET positivity in the brain.

Disclosures: **J. Park:** None. **S. Han:** None. **H. Cho:** None. **M. Byun:** None. **D. Yi:** None. **Y. Choe:** None. **S. Kang:** None. **E. Jung:** None. **S. Won:** None. **E. Kim:** None. **Y. Kim:** None. **D. Lee:** None. **I. Mook-Jung:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.06/O9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF 2011-0030740

Title: Molecular and functional signatures in a novel Alzheimer's disease mouse model assessed by 10-PLEX TMT-based quantitative proteomics

Authors: *D. KIM[1], J. PARK[2], D. HAN[3], J. YANG[2], A. KIM[2], J. WOO[2], Y. KIM[2], I. MOOK-JUNG[2]
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Abstract: To elucidate the underlying mechanisms through which amyloid beta (Aβ) and tau contribute to Alzheimer's disease (AD) pathogenesis, we herein generated a novel animal model of AD. The ADLP^{APT} mice (AD-Like Pathology) carry mutated versions of human amyloid precursor protein, human presenilin-1, and human tau; at an early age, they exhibit accelerated neurofibrillary tangles together with senile plaques, neuronal loss in the hippocampal CA1 area, and memory deficits. To characterize the generated mice, we analyzed hippocampal proteome of the ADLP^{APT} mice using state-of-the-art quantitative proteomics strategy including 10-plex tandem mass tag (TMT). In addition, bioinformatics analysis of differentially expressed proteins (DEPs) revealed that ADLP^{APT} mice experienced age-dependent active immune responses and synaptic dysfunctions. Since the ADLP^{APT} mouse is the proper model to recapitulate the main features of AD pathogenesis, these proteome data based on hippocampus serve as a novel resource for researches of Aβ-tau axis and pathophysiological changes in vivo.

Disclosures: D. Kim: None. **J. Park:** None. **D. Han:** None. **J. Yang:** None. **A. Kim:** None. **J. Woo:** None. **Y. Kim:** None. **I. Mook-Jung:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.07/O10

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The Effects of Gut Microbial Community for the pathogenesis of Alzheimer's disease animal model

Authors: *H. CHOI[1], Y. KIM[1], M.-S. KIM[2], H. KIM[1], J.-W. BAE[2], I. MOOK-JUNG[1]
[1]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [2]Kyung Hee Univ., Seoul, Korea, Republic of

Abstract: Cerebral amyloidosis and severe tauopathy in the brain are key pathological features of Alzheimer's disease(AD), resulting in reactive gliosis and behavioral abnormalities of learning and memory. Despite a strong influence of the intestinal microbiota on neurodevelopment, neurological disorder and neurodegenerative diseases, a functional link between gut microbiota and AD remains unknown. Using mice that overexpress human mutant APP/PS1 and mutant tau, we examined the impact of the host microbiome on AD pathogenesis in this study. Fecal microbiota transplantation from a healthy wild type mouse into the diseased mouse caused the microbial re-colonization and ameliorated Aβ plaque and neurofibrillary tangle formation. In addition, we also observed attenuated glial reactivity and improvement of learning behavior in these recipient animals. These findings implicated that the gut microbial community of AD model mouse is involved in the disease development. It suggests that gut microbial dysbiosis and gut microbiota-derived factors might contribute to the pathogenesis of AD.

Disclosures: H. Choi: None. **Y. Kim:** None. **M. Kim:** None. **H. Kim:** None. **J. Bae:** None. **I. Mook-Jung:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH 5P20RR016476-11

NIH 8P20GM103476-11

NIH R15AG046915

NSF 1445151

NSF 0947944

NIH P20GM103641

Title: Oligomer-to-oligomer propagation between wild-type and mutant amyloid-beta

Authors: *D. N. DEAN[1], S. Z. VANCE[2], R. P. CAMPBELL[1], M. A. MOSS[2], V. RANGACHARI[1]
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Abstract: Soluble oligomers of amyloid-β (Aβ) are the primary toxic agents responsible for neuronal dysfunction in Alzheimer disease (AD) brains. While parenchymal deposits of Aβ characterize AD, deposition in the cerebral vasculature defines a condition called cerebral amyloid angiopathy (CAA). A high incidence of CAA exits among AD patients. Mutant forms of Aβ40 and Aβ42 (Arctic, Italian, and Dutch) are known to lead to severe CAA. The co-existence of AD and CAA could suggest an interplay between WT and mutant forms of Aβ. We have previously revealed that an oligomeric strain of synthetic WT Aβ42, called LFAOs, selectively induces CAA in transgenic mice. Furthermore, we have reported a novel self-propagating oligomer that forms distinct fibrils containing the repeating oligomer unit. Here, we report a detailed kinetic mechanism for LFAO self-propagation and also show oligomer-to-oligomer cross-propagation of WT LFAOs with Arctic (E22G) Aβ42. We also show the reverse-cross-propagation of E22G Aβ oligomers with WT Aβ42 monomers. Such a mechanism of propagation produces unique hybrid aggregates containing both WT and E22G Aβ. We have investigated the ability of such a hybrid aggregate species to induce apoptosis in human neuroblastoma cells. These results will be reported and discussed.

Disclosures: D.N. Dean: None. **S.Z. Vance:** None. **R.P. Campbell:** None. **M.A. Moss:** None. **V. Rangachari:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Soc. of Manitoba

Research Manitoba

St. Boniface Hospital Research Foundation

Title: Using Nilotinib to improve mitochondrial function in Alzheimer’s disease

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Abstract: Objective: Alzheimer's disease (AD) is a progressive age-related neurodegenerative disorder. AD is also associated with the build-up of amyloid beta (AB) plaques and tau neurofibrillary tangles (NFTs) in brain tissue; however, AD is considered a multifactorial condition. The earliest deficits in the pathological progression of AD actually seem to be caused by impaired mitochondrial function - before the robust appearance of AB and NFTs. In fact, current evidence suggests there are several mechanisms that can affect mitochondrial function that are associated with normal aging and/or linked with AD and other mitochondrial disorders. In this study, we investigated the effect of the FDA-approved anti-cancer drug, Nilotinib, on mitochondrial function and evaluated mitochondrial protein subunit expression. **Methods**: Astroglia cells (microglia and astrocytes) were isolated from the brain cortices of 7 day old C57BL/6 mice (control background strain) and 3xTg mice, a transgenic model of AD. After 2-3 weeks, cells were cultured on Seahorse XF24 analyzer (Seahorse BioSciences) plates at a density of 80,000 cells/well. After 24 hrs., the oxygen consumption rate (OCR) was measured in control vs. 3xTg cells in real time using the XF24 analyzer after dose-dependent treatment with Nilotinib (10 nm-1 uM). Additionally, Western blots were used to detect expression levels of key proteins involved in mitochondrial function: nuclear factor kappa B (NF-κB) p50/p105/p65/C-rel subunits, and manganese superoxide dismutase (MnSOD), cAMP response element-binding protein (pCREB), and select oxidative phosphorylation (OXPHOS) complex protein subunits in astroglia cells in the presence and absence of Nilotinib treatment. **Results**: Our data show Nilotinib enhances mitochondrial function putatively through the up-regulation of transcription factor NF-κB, and via changes associated with antioxidant MnSOD, pCREB, and OXPHOS signaling. Both basal and maximal respiration levels were significantly increased ($p<0.05$) after a 24 hr. treatment with 100 nM Nilotinib in astroglial cells from AD mice, but not in control cells. Additionally, we found Nilotinib increased expression of NF-κB p50/p105 subunits, and pCREB, and MnSOD in AD cells and NF-κB p50/p105 subunits and pCREB in control cells. Moreover, Nilotinib increased expression of mitochondrial complex (I-V) protein subunits in 3xTg cells, but not in control cells. **Conclusions**: These results highlight a potential role for Nilotinib in regulating astroglial bioenergetics in early-stage AD and suggest that energy metabolism may be an effective therapeutic target for preventing or treating AD.

Disclosures: B.C. Albensi: None. **R.S. Turner:** None. **A. Adlimoghaddam:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.10/P3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Erasmus Mundus PhD Exchange grant

Title: The action of nobiletin on brain mitochondria and yeast cells

Authors: *N. SHARIKADZE[1,2,3], N. JOJUA[1], E. ZHURAVLIOVA[1,4], N. HAMMAD[2,3], N. AVERET[2,3], M. RIGOULET[2,3], A. DEVIN[2,3], D. G. MIKELADZE[1,4]
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Abstract: Citrus flavonoid nobiletin has anticancer, antiviral, neuroprotective, anti-inflammatory activities and depending on the cell types exhibits both pro- or anti-apoptotic properties that suggest the effect of this compound on the central metabolic systems, such as mitochondrial bioenergetics. **The aim** of our study was to investigate the possible target of nobiletin on the components of the mitochondrial respiratory chain. Our preliminary results have shown that one of possible target of nobiletin may be is complex I. Thus in this study we used isolated bovine brain mitochondria and two strains of yeast, whereas yeast foam strain exhibits two external NADH dehydrogenases and one internal NADH dehydrogenases that have no proton pumping activity, the yeast Candida utilis mitochondria exhibit a complex I that is proposed to pump protons and an external NADH dehydrogenase that does not pump protons. **Methods:** Analysis of mitochondrial enzymes' activities, estimation of respiration rate in bovine brain isolated mitochondria, mitochondrial membrane potential, ROS production were performed in bovine brain mitochondria to evaluate the direct effect of nobiletin on the mitochondrial bioenergetics, yeast strains culture medium and growth conditions, oxygen consumption assay. **Results:** We have found that nobiletin decreases oxygen consumption in the presence of glutamate and malate and increases in the presence of succinate. In parallel, nobiletin increases NADH oxidation, alpha-ketoglutarate dehydrogenase activities and alpha-ketoglutarate-dependent production of ATP. Additionally, nobiletin reduces the production of peroxides in the presence of complex I substrates and does not change succinate-driven peroxide formation. Besides, nobiletin induces transient elevation of membrane potential followed by mild depolarization. Nobiletin inhibits mitochondrial respiratory chain on whole cells in a similar fashion for Yeast foam and Candida utilis. This inhibition is partially alleviated after one hour of cells incubation in the presence of nobiletin. **Conclusion :** Nobiletin may act as a mild "uncoupler", which through activation of a-KGDH-complex and acceleration of matrix substrate-level phosphorylation maintain membrane potential at a normal level. This switch in mitochondrial metabolism could elevate succinate-driven oxygen consumption. We propose that nobiletin changes oxidative metabolism that results in respiration inhibition and could "adapt" cell to low-oxygen conditions.

Disclosures: N. Sharikadze: None. **N. Jojua:** None. **E. Zhuravliova:** None. **N. Hammad:** None. **N. Averet:** None. **M. Rigoulet:** None. **A. Devin:** None. **D.G. Mikeladze:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MUSC ‘COBRE in Lipidomics and Pathobiology’ Grant 5P30GM103339-03.

NIA, R21AG052321

Title: Perturbed sphingolipid metabolism in mouse models of type-2 diabetes and AD

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Abstract: While metabolic disorders including Type 2 diabetes (T2DM) are considered risk factors for Alzheimer’s disease (AD), increasing evidence further supports insulin resistance (IR) and mitochondrial dysfunction as key pathogenic mechanisms underlying AD in common with T2DM. Since perturbed sphingolipid (SPL) metabolism leading to increased ceramide (Cer) is known to induce such metabolic defects in peripheral tissues, it was of interest to determine brain SPL profiles in a mouse model of T2DM (-induced with a high-fat diet plus low-dose streptozotocin regimen) and a transgenic (Tg) AD model. Sphingolipidomic analysis of hippocampi from T2DM mice using HPLC-MS/MS showed that although the increase in total Cers did not reach significance, there was a significant increase in the levels of C14-Cer (1.61pmol/mg tissue protein vs. 0.825pmol/mg non-diabetic control; *p=0.005*) and C16-Cer (17.33pmol/mg vs. 9.30pmol/mg; *p=0.012*) with a parallel increase in the expression of CerS6, the enzyme that produces these Cer species. There was a reciprocal decrease in sphingosine (Sph)-1 phosphate (S1P) levels implying imbalanced 'SPL rheostat'. SPL profiles of 10mo-old PDAPP Tg showed increased hippocampal levels of C16 (13.29pmol/mg vs. 9.30pmol/mg; *p=0.032*) and C18 Cer (700.41pmol/mg vs. 389.86pmol/mg; *p=0.036*) relative to wild-type mice. Interestingly, comparative analysis of SPL profiles of younger/adult (10mo) vs. aged (18mo) Tg mice revealed an age-related shift in Cer/S1P with a drastic reduction in total Cers (from 2136pmol/mg total Cers at 10mo to 742pmol/mg at 18mo) reflecting significant decreases in individual species, vs. a striking increase in S1P (23.86pmol/mg at 18mo vs. 1.42pmol/mg at 10mo). Immunoblot analysis indicated age-dependent increased expression of acid sphingomyelinase, a Cer-generating enzyme and acid ceramidase, which converts Cer to Sph, as well as Sph kinase (type-2), which phosphorylates Sph to produce S1P. The results will be discussed in terms of the potential role of Cer in IR and/or mitochondrial dysfunction in response to hyperglycemia/hyperinsulinemia (T2DM) and to Abeta (PDAPP Tg at disease onset) as well as, age-related shift in Cer/S1P potentially contributing to amyloid accumulation and disrupted autophagic flux associated with pathological progression.

Disclosures: **N.R. Bhat:** None. **V. Paladugu:** None. **S. Mohanty:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

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Program#/Poster#: 666.12/P5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA AG038739

NINDS 082635

Title: Ascorbate deficiency and altered glutamate clearance increase seizure susceptibility and cognitive decline in a mouse model of Alzheimer's disease

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Abstract: Alzheimer’s disease is considered a disease of accelerated aging, and it is likely that pathogenic processes begin decades prior to changes in brain atrophy and cognitive decline are detected in clinic. Seizures are an important shared pathological feature of several neurodegenerative diseases that can dramatically increase cognitive decline by triggering apoptosis and cell death in hippocampus and cortical regions critical for learning and memory. Ascorbic acid (ascorbate, vitamin C) deficiency plays a critical role in pathogenic and metabolic changes that accompany seizures susceptibilty. Following glutamate uptake via the astrocyte glutamate transporter GLT-1, ascorbate is released into the synapse through volume regulated anion channels, and as such may be critical for neuronal protection against glutamate toxicity during seizures. Mice carrying familial Alzheimer’s disease mutations (APP_{SWE}/$PSEN1^{dE9}$) and ascorbate deficient mice, either through an inability to synthesize ascorbate (gulolactone oxidase knock-out mice; $gulo^{-/-}$), or through decreased ascorbate transport via heterozygous expression of the sodium vitamin C transporter, type 2 (SVCT2), are more sensitive to the seizure-inducing effects of kainic acid (10 mg/kg, i.p.) than wild-type mice, or mice with adequate ascorbate. Accelerated and prolonged response patterns were observed in both EEG and behavioral studies. Even a single mild seizure negatively impacted learning and memory in the water-maze in APP_{SWE}/$PSEN1^{dE9}$mice compared to wild-type controls, and retention of a new platform location was correlated with seizure onset latency in SVCT2-heterozygous and APP_{SWE}/$PSEN1^{dE9}$mice. Low brain ascorbate altered expression of genes involved in glutamate transport in the hippocampus, including GLT-1, GLAST and EAAC1. Chronic treatment with the beta-lactam antibiotic ceftriaxone (200 mg/kg, i.p.), which upregulates GLT-1, was protective against acute kainic acid-induced immobility. Glutamate toxicity may be particularly harmful in low ascorbate

conditions due to increased oxidative stress from mitochondrial dysfunction associated with Alzheimer's disease. Mitochondria isolated from $APP_{SWE}/PSEN1^{dE9}$mice consumed greater levels of oxygen and generated more reactive oxygen species. Furthermore, mitochondria isolated from the brains of SVCT2-heterozygous mice also generated greater levels of reactive oxidative species. Together these studies support the role of ascorbate deficiency in increased seizure susceptibility, which may be particularly relevant in Alzheimer's disease.

Disclosures: F.E. Harrison: None. **S. Dixit:** None. **D.J. Mi:** None. **T.A. Warner:** None. **J. Kang:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

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Program#/Poster#: 666.13/P6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Program for Neuropsychiatric Research, McLean Hospital, SUNDRY

Title: Late-onset Alzheimer's disease is associated with inherent changes in bioenergetics profiles

Authors: *K. C. SONNTAG, W.-I. RYU, K. M. AMIRAULT, R. A. HEALY, A. J. SIEGEL, D. L. MCPHIE, B. FORESTER, B. M. COHEN
McLean Hospital, Harvard Med. Sch., Belmont, MA

Abstract: Body-wide changes in bioenergetics, i.e., energy metabolism, occur in normal aging and disturbed bioenergetics may be an important contributing mechanism underlying late-onset Alzheimer's disease (LOAD). We investigated the bioenergetic profiles of fibroblasts from LOAD patients (n = 10) and healthy controls (n = 20, 7 age-matched to LOAD and 13 younger subjects), as a function of age and disease. LOAD cells showed impaired respiratory consumption, and an abnormal redox potential, associated with reduced expression of the complex I subunit NADH:Ubiquinone Oxidoreductase Core Subunit 4 (MTND4), but not with mitochondrial mass, transmembrane instability, the production of reactive oxygen species, or DNA deletions. LOAD fibroblasts demonstrated a shift in energy production to glycolysis, despite an impairment in increasing glucose uptake in response to IGF-1. The increase of glycolysis and abnormal redox potential in LOAD appeared to be inherent, as they were disease- and not age-specific. Our findings support the hypothesis that impairment in multiple interacting components of bioenergetic metabolism may be a key mechanism contributing to the risk and pathophysiology of LOAD.

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Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG054025

NIH Grant NS094557

Title: Toxic tau oligomeric strains targeted and modulated by novel curcumin derivatives

Authors: *F. LO CASCIO[1,2,3], U. SENGUPTA[1,2], A. PALUMBO PICCIONELLO[4], C. CAMPANELLA[3], C. CARUSO BAVISOTTO[3], A. PACE[4], R. KAYED[1,2]
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Abstract: Alzheimer’s diseases (AD) is the most common age-related neurodegenerative disorder affecting millions of people worldwide. Therefore, finding effective interventions and therapies is extremely important. AD is one of over 18 different diseases known as tauopathies, characterized by the pathological aggregation and accumulation of tau. During the disease, tau detaches from the microtubules and undergoes conformational changes leading to the formation of different types of aggregates and inclusions such as the well-characterized neurofibrillary tangles (NFTs). Recent evidences suggest that NFTs are the least toxic form of tau aggregates as compared to the smaller, soluble and dynamic tau oligomers. However, the structural and biological features of tau oligomers are still poorly understood due to their dynamic nature and conformational heterogeneity. Therefore, they can manifest in many conformations known as tau oligomeric strains. Studies focusing on the mechanisms underlying tau oligomeric strain formation and characteristics are challenging and could explain how the aggregation and accumulation of tau causes many disorders and diverse phenotypes in different individuals within the same disease. In preclinical studies, tau aggregates have been effectively targeted by immunotherapeutic approaches, aptamers and anti-sense oligonucleotides (ASO). We hypothesize that small molecules, able to target and modulate tau aggregation pathways, can be used to neutralize the formation and toxicity of the predicted large number of tau oligomeric strains, thus preventing the spread of pathology. Here, we used newly synthetized curcumin-like compounds to modulate tau oligomeric strains toxicity. We performed *in vitro* techniques including direct ELISA and Western Blot analyses as well as biophysical assays to characterize

tau oligomeric strains and their reactivity with tau oligomer specific polyclonal and monoclonal antibodies, T22 and TOMAs respectively, in the absence and presence of curcumin analogs. Our data suggest that novel curcumin derivatives are able to bind and alter tau aggregation pathways, resulting in the formation of tau structures with decreased toxicity. Based on these preliminary results, we propose that screening small molecule libraries against different oligomeric strains may lead to the discovery of new compounds which are effective against one or more tau strain and move the tau field forward. Finally, curcumin analogs could contribute both in the development of novel therapeutic approaches for AD and other tauopathies as well as imaging agents able to detect toxic tau oligomeric strains in the early stages of the disease.

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Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

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Program#/Poster#: 666.15/P8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AG054025

NS094557

Title: Differential spreading and toxicity of brain-derived tau oligomeric stains

Authors: *R. KAYED, U. SENGUPTA, M. CARRETERO MURILLO, D. CASTILLO-CARRANZA, J. GERSON
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Abstract: For a long time Tau pathology has been implicated in a number of neurodegenerative tauopathies such as Alzheimer’s disease (AD), progressive supranuclear palsy (PSP), and recently Parkinson’s disease (PD), dementia with Lewy bodies (DLB) and Huntington disease. However, each disorder is characterized by a unique combination of symptoms and other pathological hallmarks which regularly overlap. Large body of research suggest that oligomeric tau is the most toxic form of the protein and represent potent seeds causing spread of disease pathology, the focus has been on the meta-stable tau fibrillar strains. These oligomers have prion-like properties may play a disease specific role in the pathogenesis of neurodegenerative disorders. Therefore, it is of great importance to understand the ability of tau to form disease specific oligomeric strains, characterize them and investigate potentials mechanisms for their formation in different diseases and their potential role in disease phenotypes and pathophysiology. We isolated and characterized novel disease associated tau oligomeric strains

form PD, DLB, AD and PSP tissues and performed thorough biochemically, biophysically and immunological characterization. Moreover we studied the seeding potential in vitro and propagation in vivo. We found that disease associated tau oligomeric strains are capable of seeding propagating in vivo in a prion-like fashion and induced distinct speeding patterns and phenotypes in Htau mouse model. Amyloid-β, α-synuclein and other amyloidogenic proteins may affect tau strain characteristics and toxicity. The formation of different tau oligomeric strains may be responsible for different phenotypes that are disease-specific and/or overlapping. Tau and α-synuclein oligomers may have a toxic synergistic relationship. Tau and α-synuclein oligomeric structures represent main targets for therapeutic agents. Tau oligomeric strains may provide new insights into mechanisms of disease onset and diversity.

Disclosures: R. Kayed: None. **U. Sengupta:** None. **M. Carretero Murillo:** None. **D. Castillo-Carranza:** None. **J. Gerson:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG054025

NIH Grant NS094557

Title: The role of alpha-synuclein oligomeric conformations on tau aggregation and the formation of oligomeric strains

Authors: *U. SENGUPTA[1], J. GERSON[3], D. CASTILLO-CARRANZA[2], R. KAYED[1]
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Abstract: Each neurodegenerative disorder is characterized by a unique combination of symptoms and pathological hallmarks of proteinaceous aggregates. However, these aggregates and symptoms often overlap between different diseases. Tau pathology has been implicated in a number of neurodegenerative tauopathies such as Alzheimer’s disease (AD), progressive supranuclear palsy (PSP), and recently Parkinson’s disease (PD), dementia with Lewy bodies (DLB). I hypothesized that tau oligomers with prion-like properties may play a disease specific role in the pathogenesis of synucleinopathies .Therefore, I am investigating the role different synuclein oligomeric strains inducing the formation of different strains of tau oligomers in synucleinopathies and compare these different populations of tau oligomers with the classical AD and PSP brain-derived tau oligomers.

Despite the large body of research that shown oligomeric tau is the most potent and toxic form of the protein causing spread of disease pathology, the focus has been on the meta-stable tau fibrillar strains. Therefore, it is of great importance to understand the ability of tau to form disease specific oligomeric strains, characterize them and investigate potentials mechanisms for their formation in different diseases and their potential role in disease phenotypes and pathophysiology.
We isolated alpha-synuclein oligomers and tau oligomers form PD, DLB brain tissues. We also isolated tau oligomers from AD and PSP tissues and performed thorough biochemical, biophysical and immunological characterization of these brain-derived oligomers. Moreover we studied the seeding potential in vitro and propagation in vivo.
Different tau oligomeric strains induced by different synuclein oligomeric strains may be responsible for diverse and or overlapping phenotypes that are disease-specific. Tau and a-syn oligomers may have a toxic synergistic relationship. Thus oligomeric structures of these two pathogenic proteins and their interplay represent main targets for therapeutic agents.

Disclosures: U. Sengupta: None. **J. Gerson:** None. **D. Castillo-Carranza:** None. **R. Kayed:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.17/P10

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Development of sensitive, robust and quantitative assays for tau aggregation, phosphorylation and fragmentation, and their use for the characterization of tau pathology in transgenic mouse models

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Abstract: Protein Tau, and its related pathology in Alzheimer’s disease (AD) and other tauopathies, is currently under investigation in clinical and preclinical studies as a target for immunotherapeutic interventions. In this regard it is becoming increasingly important to have validated and sensitive assays to measure the development of tau aggregation, phosphorylation and fragmentation in preclinical mouse models, but also as clinical biomarker tools for measuring therapeutic efficacy in humans.
We developed and compared immunoassays to measure tau aggregation, phosphorylation and fragmentation on different platforms; meso scale discovery (MSD), AlphaLISA and ELISA. We concluded that the MSD platform, using electrochemiluminescence detection, was the most

sensitive method, displaying the largest dynamic range and very low inter- and intraplate variation. Additionally a standard was developed for the aggregation assays to allow quantification of tau aggregation.
The MSD assays that were developed, were used to characterize the progression of tau pathology in the brains of different preclinical mouse models for tauopathy. In these transgenic models, mutated human tau is overexpressed in neurons leading to increased tau phosphorylation and to aggregation of tau into tangles. The models are used to evaluate efficacy of different tau-targeting treatments but caution has to be taken when interpreting the results. The tau transgene in the mouse models is continuously expressed in abnormally high amounts in the cells and results in pathology that does not fully mimic the gradual spatial progression of tauopathy in human disease. A detailed characterization of the development of tauopathy in the transgenic models is therefore needed to determine the optimal treatment window with the best estimated translatability to the human situation.
We characterized the onset and progression of tau phosphorylation and aggregation in 3 different tau transgenic mouse models, Tau.P301L, PS19 and P301S/Bl6. The assays that were developed can play a major role for the measurement of different Tau species, not only in brain homogenates, but also in body fluids with lower tau concentrations such as interstitial fluid, blood and CSF.

Disclosures: **C. Theunis:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutica. **K. Van Kolen:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutica. **B. Van Broeck:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutica. **G. Daneels:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutica. **M. Vandermeeren:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutica. **M. Mercken:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutica.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.18/Q1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Effect of oral and intrahippocampal administration of tideglusib on the regulation of tau phosphorylation, amyloid beta peptide and memory in diabetic rats

Authors: *T. PONCE-LOPEZ[1,2], M. ABASCAL-DIAZ[2], S. GARCÍA-ANDRADE[2], A. FLORES-VIZCAYA[2], D. MURILLO-REYES[2], A. VARGAS[2]
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Abstract: Several studies have shown that patients with diabetes mellitus type 2 (DM2) are at increased risk of developing Alzheimer's disease (AD). Due to the profound socioeconomic

impact of diabetes and AD, understanding the mechanisms that could link both diseases is essential. Oxidative stress, dysfunction of glucose and cholesterol metabolism, and mitochondrial activity, among others, have been shown to be associated with diabetes and AD. In fact, patients with diabetes have cognitive impairment, beta amyloid peptide deposits and hyperphosphorylated tau protein, neuropathological features of AD. It has been associated with disorders of signal transduction of the insulin receptor (IR), termed "cerebral insulin resistance". This is analogous to peripheral insulin resistance, represented by impaired neuronal insulin functions; such as glucose regulation, growth, neuronal survival and remodeling, and assembly of microtubules. Insulin is known to regulate tau phosphorylation through the PI3K-Akt-GSK3 pathway of insulin receptor (IR), disruption of this balance leads to abnormal phosphorylation of tau and amyloid deposits. As a consequence, GSK3 inhibitors have emerged as potential therapeutic tools for neural diseases dealing the tiadiazolidindione-derivative tideglusib ATP-noncompetitive GSK3 inhibitor has been shown to induce beneficial effects in some clinical trials for AD treatment with cognitive decline. This study aims to evaluate and compare the effect (systemic and intrahippocamcal) of chronic treatment of tideglusib a memory impairments, disruption insulin receptor (IR), phosphatidylinositol-3-kinase/protein kinase B/GSK3 (PI3K-Akt/PKB-GSK3) signaling cascade, and abnormal phosphorylation of tau and Beta amyloid peptide in a DM2 model. Wistar rats were given streptozotocin (STZ; 45 mg/kg) and a high-fat diet. The oral administration of tideglusib will be for 14 days and stereotactic surgery will be performed for the intrahippocampal administration of tideglusib (50 mg/kg). The spatial memory were assessed by Morris water maze. We are quantifying peripheral insulin and lipids by the ELISA test, the insulin receptor, the Akt, GSK3 and tau protein will be through western blot in hippocampus. Results showed that tideglusib improved spatial learning and memory. This evidence will provide insight about the role PI3K-Akt/PKB-GSK3) signaling cascade of IR and the therapeutic benefits of tideglusib on abnormal phosphorylation tau and memory dysfunction to prevent the development of the AD in patients with DM2.

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Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.19/Q2

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: SUVN-D4010, a potent and selective 5-HT_4 receptor partial agonist - effect of food, gender and age on human pharmacokinetics

Authors: *G. BHYRAPUNENI, K. MUDIGONDA, R. PALACHARLA, P. JAYARAJAN, R. ABRAHAM, R. SUBRAMANIAN, V. GOYAL, S. PANDEY, D. AJJALA, A. MOHAMMED, S. JETTA, R. NIROGI
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Abstract: SUVN-D4010 is a potent, selective and orally bioavailable 5-HT_4 receptor partial agonist being developed for the treatment of Alzheimer's disease. SUVN-D4010 has shown to improve the episodic, working and emotional memory in preclinical animal models. At pharmacologically effective doses, SUVN-D4010 also produced significant increase in the brain acetylcholine and cortical sAPPα levels with simultaneous decrease in amyloid-β protein levels. SUVN-D4010 was studied in a single-center, multi-faceted, Phase 1 clinical trial (US IND) to evaluate its safety, tolerability, and pharmacokinetics after single and multiple ascending doses in healthy male subjects. For single dose evaluation, subjects were dosed with 5 mg, 15 mg, 30 mg or 45 mg of SUVN-D4010 tablets, once. For multiple ascending dose evaluation, the once daily doses of 10, 25 and 40 mg SUVN-D4010 were administered for 14 days. Additional Phase 1 clinical study (US IND) was carried out to evaluate the effects of food, gender and age on pharmacokinetics in healthy human volunteers. SUVN-D4010 was administered at a dose of 25 mg for evaluation of food, gender and age effect. Effect of food on SUVN-D4010 pharmacokinetics was evaluated under fed and fasted conditions in healthy adult male subjects. Effect of gender was evaluated in healthy adult male and female subjects under fasted conditions. For evaluation of age effect, SUVN-D4010 was administered under fasted conditions in healthy adult and elderly subjects. SUVN-D4010 was quantified in plasma using a validated LC-MS/MS method. Safety and tolerability was assessed throughout the study by the incidence and severity of AEs, abnormalities in vital signs, ECG and clinical laboratory assessments. SUVN-D4010 was well tolerated up to the highest tested dose of 45 mg single dose or 40 mg/day multiple doses in healthy male subjects. There were no clinically relevant or serious adverse events reported. During single ascending dose studies, the absorption of SUVN-D4010 was rapid and exposures (C_{max} and AUC) were dose proportional at the tested doses between 5 mg to 45 mg. During multiple ascending dose studies, Food, gender and age had no effect on human pharmacokinetics of SUVN-D4010. SUVN-D4010 has excellent safety and pharmacokinetic profile following single or multiple dose administration for 14 days in healthy male subjects. Projected efficacy concentrations of SUVN-D4010 achieved during multiple ascending dose studies and attained steady state on day 3 in healthy male subjects. Phase 2 enabling long term non-clinical safety studies for SUVN-D4010 are currently ongoing.

Disclosures: **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **K. Mudigonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **R. Palacharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India.

D. Ajjala: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **S. Jetta:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.20/Q3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Louisiana Board of Regents LEQSF (2014-19)-GF-09

Title: Effects of glucocorticoid and adenosine agonist addition on glucocorticoid receptor translocation in SH-SY5Y cells

Authors: *D. E. OSEID[1], S. LEAR[2], A. S. ROBINSON[2]
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Abstract: Multiple lines of evidence suggest a chronic upregulation of circulating glucocorticoids may be correlated with cognitive deficits and Alzheimer’s disease (AD). Since glucocorticoids may have an impact on the lipid bilayer (Oliveira, T.G. 2016; Dindia, L., 2012), we hypothesized that the effect of glucocorticoids related to AD are an effect of fluidization of the lipid bilayer that then stimulates unliganded glucocorticoid receptor (GR) translocation to the nucleus. Here, we have monitored nuclear translocation of the cytosolic GR in SH-SY5Y human neuroblastoma cells using live-cell imaging of a GR-GFP fusion protein, reported in previous studies (Muglia L.J., 2002). In contrast to our expectation, fluidizing the membrane with 25 mM benzyl alcohol and depleting membrane cholesterol with 5 mM methyl-β-cyclodextrin did not induce nuclear translocation of GR-GFP. Interestingly, a BSA-conjugated dexamethasone (Dex-BSA) stimulated nuclear translocation of GR-GFP, but at a significantly slower rate than free cortisol. This result suggests that there is steroid action at the level of the membrane that induces unbound cytosolic GR to traffic to the nucleus, and this mechanism likely does not involve bulk changes to membrane bilayer rigidity. In follow-up studies, we investigated a possible interaction between the adenosine $A_{2A}R$ receptor and GR, which has been recently supported through evidence of transcriptional activation of GR with $A_{2A}R$ agonists (Batahala, V.L., 2016). In our studies, adenosine $A_{2A}R$ activation with the agonist CGS21680 was not sufficient to induce rapid translocation of GR-GFP after fifty minutes. Taken together, these results suggest there is an undetermined mechanism at the membrane for rapid, unliganded GR nuclear translocation that likely does not directly involve changes to membrane fluidity or $A_{2A}R$ signaling.

Disclosures: **D.E. Oseid:** None. **S. Lear:** None. **A.S. Robinson:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.21/Q4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The relationship between insulin resistance and amyloid pathology in diabetic AD model mice

Authors: *K. MATSUI[1], K. YAMAGUCHI[1], A. MANO[1], T. SANO[1], T. HASHIMOTO[1], T. KUBOTA[2], N. KUBOTA[2], T. KADOWAKI[2], T. WAKABAYASHI[1], T. IWATSUBO[1]
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder pathologically characterized by the deposition of amyloid β (Aβ) in the brain. Recent large-scale epidemiological studies revealed that type 2 diabetes mellitus (T2DM) increases the risk of dementia including AD. Although glucose intolerance and insulin resistance have been associated with augmentation of amyloid pathology, the molecular mechanism that links T2DM and AD in brain remains unclear. To elucidate the mechanism of AD progression by T2DM, we generated APP transgenic mice (A7 line) fed with high-fat diet (HFD) for 2, 6 and 12 months. HFD-fed A7 mice recapitulated diabetic phenotypes including elevated body weight, blood glucose and insulin levels, as well as insulin resistance. HFD feeding also induced increased expression of TNFα in the periphery. In addition, both 5 and 9-months-old HFD-fed A7 mice displayed reduced insulin response in the brains. Histopathological and biochemical analyses revealed that Aβ levels and amyloid deposition were significantly increased in the brains of 15-months-old HFD-fed mice compared to those fed with normal diet. To gain insights into the mechanism of increase in Aβ levels by metabolic overloading, we examined de novo Aβ secretion in acute slice cultures of the brains. Slices of 9-months-old HFD-fed A7 mice, at an age prior to the start of Aβ deposition, did not display changes in Aβ secretion. We next examined the effect of diabetic phenotypes on AD pathology in A7 mice genetically lacking insulin receptor substrate 2 (IRS-2), which displayed DM phenotypes in the periphery, i.e. hyperinsulinemia, hyperglycemia and insulin resistance. Although the Aβ levels did not change in IRS-2 deficient A7 mice at 5 months of age, Aβ deposition was significantly decreased in the brains of those at 15 months of age. IRS-2 deficient A7 mice also did not display changes in Aβ secretion level from brain slices at 5 months of age before Aβ deposition starts. In contrast to the HFD-fed A7 mice, A7 mice did not show elevated expression of TNFα in the adipose tissue by IRS-2 deficiency. We therefore examined whether metabolic loading would increase Aβ

deposition in IRS-2 deficient A7 mice. As a result, long-term HFD-feeding in IRS-2 deficient A7 mice led to a significant increase in Aβ deposition compared to those fed with normal diet. These results suggest that causal factors in the development of insulin resistance, e.g., chronic inflammation or stress responses, rather than hyperinsulinemia, hyperglycemia and reduced insulin responsiveness, might be associated with accelerated Aβ pathology in the brains of HFD-fed AD model mice.

Disclosures: **K. Matsui:** None. **K. Yamaguchi:** None. **A. Mano:** None. **T. Sano:** None. **T. Hashimoto:** None. **T. Kubota:** None. **N. Kubota:** None. **T. Kadowaki:** None. **T. Wakabayashi:** None. **T. Iwatsubo:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.22/Q5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: University Start-up Funding #R9321

NIH (NS71022)

Title: Insulin resistance mediates neuronal cell cycle re-entry, dysfunction and degeneration

Authors: *H. CHOW[1,2], A. CHENG[1], K. HERRUP[1]
[1]Div. of Life Sci., The Hong Kong Univ. of Sci. and Technol., Hong Kong, Hong Kong; [2]Inst. for Advanced Study., The Hong Kong Univ. of Sci. and Technol., Hong Kong, Hong Kong

Abstract: Several longitudinal studies have suggested that the risk of developing Alzheimer's disease (AD) is almost double in patients with insulin resistance. There are many paths to develop insulin resistance, and prolonged hyperinsulinemia is a major one. Although insulin import from the periphery to the brain is reduced in AD, this may yet be a consequence rather than the cause as hyperinsulinemia is most often observed before the disease onset. We wished to understand the chronic effect of high to saturated levels of insulin such as that seen during the early pre-clinical stages of AD when the blood brain barrier remains fully functional for insulin import. We find that wild type, non-diabetic mice with higher plasma insulin levels show elevated levels of insulin in cerebrospinal fluid, markers of neuronal insulin resistance and impaired immediate early gene responses upon novelty exposure. In culture, prolonged insulin exposure induces cell cycle re-entry, loss of neurite branching and reduced synaptic density. Our data suggest a direct pathogenic link between peripheral hyperinsulinemia, elevated cerebrospinal fluid insulin levels and neuronal dysfunction. The early appearance of hyperinsulinemia in the progression of AD leads us to hypothesize that the shutdown of the

blood brain barrier might be a homeostatic mechanism to avoid further insulin-induced neuronal damage.

Disclosures: H. Chow: None. **A. Cheng:** None. **K. Herrup:** None.

Poster

666. Alzheimer's Disease: Biomarkers, Metabolism, and Proteomics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 666.23/Q6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MOP-43232

Fonds de Recherche Sante Quebec

Title: Folate metabolism disturbances in aging mice: A mouse model for sporadic Alzheimer's disease?

Authors: *R. BAHOUS[1], M. COSÍN-TOMÁS[3], L. DENG[1], M. PALLÀS[3], P. KALIMAN[4,5], R. ROZEN[1,2]
[1]Human Genet., [2]Dept. of Pediatrics, McGill Univ., Montreal, QC, Canada; [3]Pharmacol. Unit, Fac. of Pharmacy, Inst. de Neurociència Univ. de Barcelona (IBUB), Nucli Universitari de Pedralbes, Barcelona, Spain; [4]Inst. of Biomed. Investigation of Barcelona, Spanish Natl. Res. Council, Barcelona, Spain; [5]Ctr. for Mind and Brain, Univ. of California Davis,, Davis, CA

Abstract: Folate is an important B vitamin required for methylation reactions, nucleotide synthesis and maintenance of homocysteine at nontoxic levels. It is also essential for neuronal survival and neurotransmitter synthesis. Disturbances in folate metabolism can be genetic or dietary. They result in hyperhomocysteinemia (HHcy) and methylation disturbances, which may impact risk for Alzheimer’s disease (AD). There is a common polymorphism in an important gene in the folate pathway, methylenetetrahydrofolate reductase *(MTHFR),* which is required for homocysteine lowering and generation of the methyltetrahydrofolate used in methylation. Individuals homozygous for the *MTHFR* 677C>T polymorphism represent approximately 10-15% of many populations in North America and Europe, and have mild HHcy. Low folate intake can also result in HHcy. Many studies have used transgenic mouse models of AD in combination with low folate diets to elucidate the mechanisms by which HHcy can contribute to AD pathology. However, these models do not recapitulate the sporadic cases of AD. In our study, we fed our *Mthfr*-deficient mouse model with control or folate-deficient diets, to assess the impact of genetic and nutritional causes of HHcy, and their potential interaction, on features of AD. Memory was assessed in these mice at 8 and 10 months of age using the novel object recognition test (NOR) and the Y-maze, and anxiety was measured using the open field test. In the 10-

month-old mice, short-term memory impairment and decreased cortical expression of the neurotrophic factor *Brain derived neurotrophic factor* (*Bdnf*) was observed due to the *Mthfr*$^{+/-}$ genotype. We also observed increased expression of *Presenillin-1* (*Psen1*), in cortex of folate-deficient 10-month-old mice. Importantly, increased *Psen1* can result in amyloid plaque deposition, which is a hallmark of AD. Moreover, DNA methylation of the aforementioned genes was examined by pyrosequencing, and we observed a negative correlation between methylation levels at the promoter and gene expression. Additional experiments are in progress to further assess the specific contributions of disturbances in folate metabolism to AD pathology.

Disclosures: R. Bahous: None. **M. Cosín-Tomás:** None. **L. Deng:** None. **M. Pallàs:** None. **P. Kaliman:** None. **R. Rozen:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.01/Q7

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: SUVN-502 + donepezil + memantine (triple combination) for the symptomatic treatment of Alzheimer’s disease

Authors: *R. V. NIROGI, K. MUDIGONDA, J. RAVULA, G. BHYRAPUNENI, V. BENADE, N. MUDDANA, V. PALACHARLA, D. AJJALA, V. GOYAL, S. PANDEY, J. FERNANDES, R. ABRAHAM, P. JAYARAJAN, R. KAMBHAMPATI, K. KANDUKURI, A. SHINDE
Suven Life Sci., Hyderabad, India

Abstract: SUVN-502 is a pure 5-HT_6 receptor antagonist. SUVN-502 is being evaluated in a phase 2a multicenter, randomized, double-blind, parallel group, 26-week, placebo-controlled study. This study is regulated by US FDA. A total of 537 subjects with moderate Alzheimer's disease receiving stable doses of donepezil HCl and memantine HCl are being recruited. Subjects will receive placebo or SUVN-502 (50 or 100 mg) on top of stable doses of donepezil and memantine for 26 weeks. Rationale for phase 2 study: The effect of SUVN-502 + donepezil + memantine combination was evaluated in animal models for procognitive property (Morris water maze task), acetylcholine modulation (microdialysis) and theta modulation (electrophysiology). Co-treatment of SUVN-502 with donepezil and memantine significantly potentiated the procognitive effects when compared with memantine and donepezil treatment in the Morris water maze task. SUVN-502 potentiated the effects of donepezil and memantine combination in hippocampal acetylcholine levels and brain oscillatory activity. There were no significant changes in the exposures of SUVN-502 or donepezil or memantine. SUVN-502 + Donepezil +

Memantine represent a promising new approach for symptomatic treatment of Alzheimer's disease.

Disclosures: R.V. Nirogi: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Mudigonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **J. Ravula:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Muddana:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Palacharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **D. Ajjala:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **J. Fernandes:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Kambhampati:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Kandukuri:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.02/Q8

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: SUVN-G3031: A potent and selective histamine H_3 receptor inverse agonist -effect of food, gender and age on human pharmacokinetics

Authors: *N. MUDDANA, G. BHYRAPUNENI, K. MUDIGONDA, P. JAYARAJAN, R. ABRAHAM, R. SUBRAMANIAN, V. GOYAL, S. PANDEY, D. AJJALA, A. SHINDE, J. RAVULA, R. NIROGI
Suven Life Sci. Ltd., Hyderabad, India

Abstract: SUVN-G3031, a potent and selective histamine H_3 receptor inverse agonist is being developed for the treatment of cognitive deficits associated with Alzheimer's disease. SUVN-G3031 demonstrated cognitive enhancement and relevant neurochemical changes without affecting the sleep in rodent models. SUVN-G3031 was studied in a single-center, multi-faceted, Phase 1 clinical study (US IND) to evaluate the effects of food, gender and age on pharmacokinetics in healthy human volunteers. SUVN-G3031 was administered at a dose of 6 mg for evaluation of food, gender and age effect. Effect of food on SUVN-G3031

pharmacokinetics was evaluated under fed and fasted conditions in healthy adult male subjects. Effect of gender was evaluated in healthy adult male and female subjects under fasted conditions. For evaluation of age effect, SUVN-G3031 was administered under fasted conditions in healthy adult and elderly subjects. SUVN-G3031 was quantified in plasma using a validated LC-MS/MS method. Safety and tolerability was assessed throughout the study by the incidence and severity of AEs, abnormalities in vital signs assessments. SUVN-G3031 was well tolerated up to the highest tested dose of 20 mg/day single dose or 12 mg repeated dose in healthy adult subjects. There were no clinically relevant or serious adverse events reported by any subject during the Phase 1 study. During single ascending dose studies, exposures (C_{max} and AUC) of SUVN-G3031 were observed to be dose-proportional at the tested doses between 0.1 mg to 20 mg. SUVN-G3031 was tolerated up to the highest tested dose of 20 mg/day following single oral administration in healthy adult subjects. During multiple ascending dose studies, SUVN-G3031 has shown an excellent pharmacokinetic profile. SUVN-G3031 achieved the projected efficacy concentrations and attained steady state on day 6 in the tested population. Food, Gender and Age had no effect on human pharmacokinetics of SUVN-G3031. There were no clinically relevant or serious adverse events observed at any of the doses tested. SUVN-G3031 has excellent safety and pharmacokinetic profile after single and multiple dose administration for 14 days in healthy human volunteers. Projected efficacy concentrations of SUVN-G3031 were achieved during multiple ascending dose studies and attained steady state from day 6 in healthy male subjects. Food, Gender and Age had no effect on human pharmacokinetics of SUVN-G3031. Phase 2 enabling long term non-clinical safety studies for SUVN-G3031 are currently ongoing.

Disclosures: **N. Muddana:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **K. Mudigonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **D. Ajjala:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **J. Ravula:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd., Hyderabad, India.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.03/Q9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NHLBI Grant R37 HL063762

NIA Grant RF AG053391

NINDS and NIA Grant RO1 NS093382

Consortium for Frontotemporal Dementia Research (A108400), and the Brightfocus Foundation Grant A2016396S

Title: Increasing progranulin expression with novel small molecules

Authors: *R. J. TESLA[1], K. S. YOO[2], B. CENIK[3], J. PRANGE-KIEL[4], J. M. READY[5], N. S. WILLIAMS[5], G. G. YU[6], J. HERZ[2]
[2]Mol. Genet., [3]Psychiatry, [4]Cell Biol., [5]Biochem., [6]Neurosci., [1]Univ. of Texas, Southwestern, Dallas, TX

Abstract: Frontotemporal dementia (FTD) is the second most frequent type of presenile dementia. Loss-of-function mutations in the progranulin gene (GRN) reduces levels of the secreted glycoprotein Progranulin (PGRN) and causes FTD. Our goal is to discover small molecules that normalize PGRN protein levels in the brain, protecting GRN haplo-insufficient individuals from FTD. We screened 200,000 novel small molecules for the ability to increase PGRN in vitro utilizing a luciferase reporter. Of the 200,000 compounds, 2144 compounds showed at least a two-fold increase in luciferase activity. We chose 1280 of the most active compounds for a confirmation of activity and investigation of toxicity. In a second screen the top 130 compounds with the highest activity were tested in Neuro2A cells. We found a total of nine hits which increased PGRN levels by at least two-fold. We then used osmotic pumps to deliver our top compounds directly into the brain using intracerebroventricular cannulation. GRN Heterozygous mice were treated with vehicle (artificial cerebrospinal fluid+10% DMSO) or compound for seven days. Tissue samples were probed for changes in PGRN protein levels. Four of the nine compounds showed significant increases in PGRN levels compared to vehicle. We next investigated the pharmacokinetic properties of our lead compounds. The initial findings revealed that all three compounds penetrated the blood brain barrier and accumulated at pharmacologically effective levels. Medicinal chemistry refinement is ongoing.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.04/Q10

Topic: C.01. Brain Wellness and Aging

Support: Capes - Brazil

Title: P. cattleianum extract prevents neurochemical alterations observed in metabolic syndrome

Authors: *A. G. BARSCHAK[1], P. S. OLIVEIRA[2], M. S. P. SOARES[2], N. P. BONA[2], P. G. DA SILVA[2], J. S. CARDOSO[2], C. L. LENCINA[2], R. M. SPANEVELLO[2], F. M. STEFANELLO[2]
[1]DCBS, UFCSPA, Porto Alegre, Brazil; [2]Univ. Federal de Pelotas, Pelotas, Brazil

Abstract: Metabolic syndrome (MetS) is characterized by a combination of cardiovascular risk factors including hyperglycemia, insulin resistance, dyslipidemia and visceral obesity. Data in the literature suggests that increased energy intake can enhance the production of reactive oxygen species, which has been directly related to MetS complications and to development of neurological and neuropsychiatric disorders such as depression. Besides, acetylcholine-mediated neurotransmission is crucial to central nervous system function. Its inhibition is associated to progressive deterioration of cognitive, autonomic and neuromuscular functions. Bioactive compounds of *P. cattleianum* have demonstrated beneficial effects on alterations observed in the MetS. In the present study we investigated the effect of *P. cattleianum* fruit extract in neurochemical and behavioral parameters in rats fed with highly palatable diet (HPD). Rats were divided into 4 experimental groups and treated for 150 days: (1) received standard chow and water orally, (2) standard chow and *P. cattleianum* extract (200 mg/kg, p.o), (3) HPD and water orally, (4) HPD and *P. cattleianum* extract (200 mg/kg, p.o). Our results showed that HPD consumption increased the immobility time in forced swim test (FST) indicating depressive-like behavior. However, treatment with *P. Cattleianum* extract prevented this behavior alteration. We also observed that HPD did not modify the locomotion demonstrating that the increase in immobility time in FST is not related to the locomotor activity. In addition, *P. cattleianum* treatment prevented increased acetylcholinesterase (AChE) activity in prefrontal cortex caused by HPD consumption. In summary, our results demonstrate that *P. cattleianum* extract showed antidepressant-like and neuroprotective effects in an animal model of MetS, suggesting that *P. cattleianum* extract can be a potential therapeutic agent for individuals with this syndrome.

Disclosures: A.G. Barschak: None. **P.S. Oliveira:** None. **M.S.P. Soares:** None. **N.P. Bona:** None. **P.G. da Silva:** None. **J.S. Cardoso:** None. **C.L. Lencina:** None. **R.M. Spanevello:** None. **F.M. Stefanello:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.05/Q11

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Anticonvulsant and neuroprotective effects of cannabidiol in immature rats

Authors: *L. K. FRIEDMAN[1], J. P. WONGVGRAVIT[2]
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Abstract: Appropriate antiepileptic drugs (AEDs) for specific age groups with epilepsy are presently unavailable due to poor understanding of how early-life seizures affect the brain at critical stages in development. Cannabidiol (CBD), the major non-psychoactive constituent of marijuana which has low affinity for cannabinoid receptors, reduces seizure frequency in adult experimental epilepsy models by unknown action. Less is known about the anticonvulsant effects of CBD in the immature brain. Two models were examined on postnatal (P) day 20. Kainic (KA) acid was either injected unilaterally into the hippocampus (KAih) or systemically (KAip) to induce status epilepticus (SE). Intrahippocampal CBD was co-administered (KA+CBDih) or followed KAih after onset to SE (KA/CBDih). Sytemic CBD followed KAip 30 min after onset to SE (KA/CBDip). KA+CBDih was most efficacious to lessen seizure severity but seizures were also attenuated by KA/CBDih or KA/CBDip. The electroencephalogram (EEG) revealed reduced spike amplitude and frequency without high burst ossicillations. Hyper-locomotion of open field activity was reversed by KA+CBDih and systemic post-seizure delivery. Nissl stains and NeuN immunohistochemistry revealed neurons throughout the hippocampus of KA+CBDih treated animals had regular morphology and most resembled the controls. Similarly, after KA+CBDih, a significant percentage of reactive astroglia were less intense and fewer in number within the vulnerable CA1 and deep proliferative dentate hilar regions compared with the other treatment groups. Somatic labeling of interneurons with PV was hardly affected after KAip. In contrast, dendrtic staining was reduced or absent after KAih or KA/CBDih and increases in ipsilateral dendritic/ neuropil density were observed. Cannabinoid receptor 1 (CB1) immunodensity was minimally affected after KAih or KA/CBDih and even more steady after KA+CBDih, which contrasts elevations observed after KAip. Intrahippocampal seizure data suggest that CBD is more effective in certain types of epilepsies with hippocampal origin and/or focus rather than when extra-hippocampal amygdala/cortical structures are triggered by systemic treatments. Higher and more frequent dosing may increase peripheral efficacy. The developmental stability of CB1 expression in both seizure models implies that they play important neuroprotective roles in regulating the hippocampal seizure threshold at young ages before neurotoxicity becomes progressive and irreversible.

Disclosures: **L.K. Friedman:** None. **J.P. Wongvgravit:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.06/Q12

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Niemann-Pick Foundation

Wylder Nation Foundation

SAF-2014-57539-R

R01NS073940

Title: Preclinical development of gene therapy for Niemann Pick disease type A

Authors: L. SAMARANCH[1], A. PEREZ-CAÑAMAS[2], J. BRINGAS[1], B. SOTO-HUELIN[2], W. SAN SEBASTIAN[1], J. JURADO-ARJONA[2], J. AVILA[3], E. H. SCHUCHMAN[4], H. CHEN[5], J. R. FORSAYETH[1], M. LEDESMA[2], *K. S. BANKIEWICZ[1]
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Abstract: Background: Niemann-Pick disease type A (NPD-A) is a lysosomal storage disorder characterized by neurodegeneration and death in early childhood. It is caused by loss of function mutations in the gene encoding acid sphingomyelinase (ASM), which hydrolyzes sphingomyelin. Enzyme replacement therapy has proven successful to treat NPD-A peripheral symptoms but not brain pathology. To date, gene therapy using direct brain injection of different serotypes of adeno associated viral vectors (AAV) carrying a functional copy of the human ASM cDNA has showed limited success in the knockout ASM mouse model (ASMko). As well, few experiments using the same strategy have been performed in non-human primates (NHP), but levels of transfections were only limited to the injection site and inflammation was found.
Objective: We evaluated the safety of cerebellomedullary cistern (CM) injection of AAV serotype 9 encoding human ASM (AAV9-hASM) in NHP and its therapeutic benefit in the ASMko mouse model.
Methods: AAV9-hASM vector was delivered into the CSF throughout the CM into NHP and ASMko mouse model. After 21, 30 and 90 days, monkey brains were collected and levels of transduction were evaluated by histological immunostaining. Standard immune markers as vascular infiltration, microglia reaction or astrocytic activation were also evaluated as part of the safety assessment. Similar vector dose (adjusted by weight) was injected into ASMko CM also

by stereotactic-guided injection. Behavioral, biochemical and enzymatic analyses were performed to assess efficacy.
Results: AAV9-hASM CM injection in NHP resulted in transgene expression in brain cells along the anteroposterior axes, including cerebellum, without significant inflammatory response in all survival times evaluated. ASMko mouse experiments revealed that vector dose tested was efficacious, showing motor and memory skills improvement, with no sphingomyelin accumulation and neuronal death.
Conclusion: Our results support CM injection for future AAV9-based clinical trials in NPD-A as well as other monogenic lysosomal storage brain disorders.

Disclosures: L. Samaranch: None. **A. Perez-Cañamas:** None. **J. Bringas:** None. **B. Soto-Huelin:** None. **W. San Sebastian:** None. **J. Jurado-Arjona:** None. **J. Avila:** None. **E.H. Schuchman:** None. **H. Chen:** None. **J.R. Forsayeth:** None. **M. Ledesma:** None. **K.S. Bankiewicz:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.07/R1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Neurocure Cluster of Excellence

Title: Effects of a specific Histone Deacetylase (HDAC) inhibitor, on neuronal health and rescue of transcription in a primary neuronal culture model of Huntington’s disease

Authors: *A. N. ABDO[1], M. LOPES[1], F. PARASKEVOPOULOU[2], C. ROSENMUND[2], F. YILDIRIM[1]
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Abstract: Huntington’s disease (HD) is a progressive, fatal, autosomal dominant hereditary, neurodegenerative disorder which affects the central nervous system. Previous studies showed massive downregulation of many key genes in HD models. Here we investigated the molecular and the morphological effects of a histone deacetylase inhibitor (HDACi) targeting HDAC class I subtype 1 and 3. We investigated its potential beneficial effects in HD cell culture model and evaluated its effects on downregulated key genes and neuronal morphological parameters (Soma size, dendritic length and synapse number). We used Lentivirus-expressing mutant- (Mut-Htt) and wild-type-Huntingtin (WT-Htt) exon 1 in neuronal cultures as an *in vitro* model of HD. After 24 hour incubation with the HDAC inhibitor, several cell cytotoxicity/viability tests were performed and reverse transcriptase quantitative real-time PCR was carried out to assess levels

of expression of five key genes (BDNF, Egr1, Arc, C-fos and synaptophysin) in cortical cells and (Darpp32, DrD1, DrD2, synaptophysin, Egr1) in striatal cells. We also checked the differences in morphology and synaptic density in the cultures upon HDACi treatment via staining the cultures with neuron-specific marker MAP2 and vesicular GABA transporter VGAT. We detected a significant difference in the expression levels of the tested genes known to play a crucial role in growth and differentiation of both cortical and striatal neurons. We detected beneficial effects of HDAC inhibition where the cell viability was enhanced in HDACi-treated mutant Htt cultures compared with untreated mutant Htt cultures. We also detected significant beneficial effects on the morphology of the neurons and the expression of VGAT, comparing the mutant cultures versus mutant treated cultures, suggesting promotion of synaptic connectivity by HDACi treatment. We are currently conducting further assays to fully assess the neuroprotective potentials of this specific HDAC inhibitor in the R6/1 model via a battery of behavioural assessments, mouse brain imaging tools and RNA sequencing to elucidate the extent of the transcriptional rescue by this agent.

Disclosures: **A.N. Abdo:** None. **M. Lopes:** None. **F. Paraskevopoulou:** None. **C. Rosenmund:** None. **F. Yildirim:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.08/R2

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: VA Merit Review CP252

NIDDK R01DK080782

MVMREF

Title: The Impact of running wheel exercise on ceramide-induced cognitive decline

Authors: *C. WANG[1,3,5], J. HOFMEISTER[1,3], C. J. BILLINGTON[2,6,5], C. M. KOTZ[7,4,5,1]
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Abstract: Background: Consumption of diets high in saturated fats is an important risk factor for cognitive impairment. Ceramides, synthesized de novo from saturated fatty acids, are elevated in brain along with aging and Alzheimer's disease, and an increased ceramide level has been

suggested as a biomarker for mild cognitive impairment and AD. Previously we found that: 1) a high fat diet impaired rodents' learning ability; 2) reducing ceramide production (with myriocin) attenuated palmitate-induced apoptosis in hippocampal cells *in vitro*; 3) ceramide directly reduced viability in hippocampal cells *in vitro*; 4) *in vivo* peripheral injection of C6-ceramide led to cognitive decline; and 5) exercise could reverse high fat diet impaired cognitive decline . These data suggest mediation of ceramide in high saturated fat induced cognitive decline, and potential protection of exercise. In this experiment, we determine the impact of exercise on peripheral ceramide induced cognitive decline and immunohistochemistry change in the hippocampus.
Methods: SD male rats were divided into vehicle (Veh) and C6-ceramide (C6, 2 μg/kg) treatment groups, based on even distribution of body weight, fat mass, and baseline of cognitive evaluation (task for two-way active avoidance, TWAA). The treatment was given (IP) every other day for 14 injections. Then based on even distribution of cognition scores and body mass, both Veh and C6 groups were further divided into sedentary (Sed) and running wheel exercise (RW) subgroups: Sed_Veh, RW_Veh, Sed_C6, and RW_C6. TWAA was tested once per week. Following 4-week of exercise the animals were perfused, and hippocampal immunohistochemistry is processed for ceramide-induced hippocampal injury and cellular signaling for exercise-induced cognitive improvements.
Results & Conclusion: learning impairment occurred at three-week of IP ceramide injections, indicated by increased escape latency and failures (no escape response) vs. Veh treatment. Compared to Sed_C6 rats, RW_C6 rats showed significant reduction in escape latency and failures since week two of exercise. RW_C6 rats also showed significant reduction in escape latency and failures, compared to their pre-intervention baseline. Thus exercise exerts a neuroprotective effect against cognitive decline induced by ceramide. Currently the analysis for hippocampal immunohistochemistry is in processing.

Disclosures: C. Wang: None. **J. Hofmeister:** None. **C.J. Billington:** None. **C.M. Kotz:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.09/R3

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: CHDI Foundation

Title: Development and validation of immunoassays measuring TrkB phosphorylation and downstream signaling

Authors: *S. DIJKSTRA[1], P. HALONEN[1], J. VEENMAN[1], F. ALBERTUS[1], G. FLYNN[1], R. VAN DE BOSPOORT[1], D. F. FISCHER[2], G. MCALLISTER[2], J. A. BARD[3], I. MUNOZ-

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[1]Charles River, Leiden, Netherlands; [2]Discovery, Charles River, Saffron Walden, United Kingdom; [3]CHDI Management/CHDI Fndn., Princeton, NJ; [4]CHDI Management/CHDI Fndn., Los Angeles, CA

Abstract: Impaired BDNF - TrkB signaling has been implicated in the pathology of neurodegeneration, and in particular Huntington's Disease (HD), a monogenetic neurodegenerative disorder caused by a CAG expansion in the HTT gene. Therefore, therapeutic strategies aimed at identifying TrkB agonists are actively being pursued. Whereas assays measuring downstream effects of TrkB activation (such as the CellSensor platform) are available to support such efforts, assays measuring TrkB activation more proximally thus far are not. We therefore aimed to develop immunoassays for quantitatively measuring TrkB phosphorylation in cell and tissue lysates using the Mesoscale Discovery (MSD) platform, and to apply these in cell-based assays for low-throughput characterization of TrkB agonism of potential therapeutics. A range of antibodies was first characterized by western blot, using lysates of CellSensor Trk reporter cell lines and rodent brain samples stimulated with BDNF or vehicle. Selected antibodies were then tested in MSD assays in different combinations and orientations for capture and detection, resulting in selection of one combination for detection of phosphorylated TrkB (p-TrkB) and two combinations for total TrkB. Applying these TrkB MSD assays we found a time and concentration-dependent increase of TrkB phosphorylation in CellSensor TrkB cells and rat primary neurons upon treatment with BDNF. Similar TrkB activation kinetics were found with an agonist TrkB antibody (38B8). To assess downstream signaling induced by BDNF and 38B8 antibody we also configured commercially available AlphaLISA bead-based immunoassays for measurement of total and phosphorylated ERK1/2 and Akt. Compared to TrkB phosphorylation, kinetics were similar for Akt phosphorylation but delayed for ERK phosphorylation. In conclusion, we successfully developed sensitive immunoassays for quantification of TrkB phosphorylation that can be used to show target engagement of TrkB agonists in cell lysates and preclinical samples.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.10/R4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: A generous donation to the Brown Institute for Brain Sciences

Title: Age related changes in cognition in a rodent model of hydrocephalus

Authors: *D. L. POETA[1], H. A. BOUNDS[1], P. M. KLINGE[3], R. D. BURWELL[1,2]
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Abstract: Normal pressure hydrocephalus (NPH) is a cerebrospinal fluid (CSF) disorder resulting from abnormal CSF absorption and its accumulation in the ventricles of the brain. The accumulation of CSF results in enlarged ventricles (ventriculomegaly) and damages surrounding brain tissue. NPH patients exhibit cognitive impairments in memory and executive functioning as well as gait abnormalities such as short, shuffling steps and wide stance (reviewed in Peterson et al. 2016). Because NPH is highly correlated with age and the aging brain is vulnerable to disease and dementia (Li et al, 2013; Martinelli et al, 2013), age may play an important role in the severity of NPH symptoms. The nature and causes of these symptoms, particularly the cognitive dysfunction, is still unknown, and there are limited studies using animal models of NPH that address this open question. Previously, the rat kaolin model of hydrocephalus was shown to cause ventriculomegaly and anatomical changes involving hippocampal structures (Klinge et al, 2003) that are similar to those found in NPH patients. In the present study, we employed this model to examine the cognitive and gait impairments associated with NPH and whether such deficits are more severe with age of onset.
Adult male Long Evans rats were separated into two age groups, young and middle-aged. The young cohort of animals was 3 months old (n=13), while the middle-aged cohort was 10 months old (n=13) at the time of surgery. Rats received either a sham surgery or kaolin injection via the cisterna magna to induce hydrocephalus. After recovery, cognitive and motor impairments were assessed with a battery of tasks: 3-Dimensional Spontaneous Object Recognition (3D SOR), gait analysis, open field, and contextual fear conditioning. All rats underwent an MRI scan to verify ventricle size. In both cohorts, NPH rats showed gait deficits such as shortened stride length and increased number of falls. Interestingly, in the 3D SOR task, recognition memory was significantly impaired in middle-aged NPH animals, but not in the young NPH animals. Because there was no significant difference in locomotor activity, this decline in performance can be attributed to age. Our interpretation is that younger subjects are more resilient to cognitive impairments. We will continue to investigate this effect of age by using other cognitive tasks involving regions known to be affected by NPH, such as the hippocampus, parahippocampal, and prefrontal cortices.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.11/R5

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: PAPIIT IG201014

Title: Diurnal variations of glutamateric system in brain motor cortex in rat

Authors: *F. E. ROJO[1], V. ARRIAGA[2], R. GUEVARA-GUZMÁN[2], M. MARTÍNEZ-VARGAS[2], L. NAVARRO[2], E. COBALLASE-URRUTIA[3], L. CARMONA-APARICIO[3]
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Abstract: Introduction: The glutamatergic system is the principal excitatory factor in the brain, is involved in process like excitotoxicity after a Traumatic brain injury (TBI)or a ischemic process is a major public health problem. Previous data from our laboratory suggests that recovery from a TBI depends on the time that TBI is induced. The study shows how the glutamic system varies both in the expression of the NMDA receptor (NMDAR) and in the release of glutamate, along to the time of the day, which may have implications for the processes of damage and neuroprotection that occur after trauma or ischemia process.
Method: Wistar rats were subjected to TBI at different times of day and their recovery was analyzed 24 hours later. We also analyzed NMDAR expression in the cerebral cortex via western blotting in control rats killed at different hours of the day and in rats subjected to TBI and killed 24 hours after. We also analyzed de glutamate release along to the day by microdialisis technic.
Results: Our results show that both; NMDAR expression and release of glutamate in the cerebral cortex rats shows a trend toward maintaining a diurnal rhythm. NMDAR expression in the cerebral cortex shows a diurnal rhythm in rats subjected to TBI at different hours of the day, with minimum expression in the hours of darkness. In the other hand the glutamate released in control rats show a diurnal variation.
Conclusions: Both NMDAR expression and released of glutamate appears to follow a diurnal rhythm in the cerebral cortex, which in turn modulates excitotoxicity; this may explain why TBI recovery is dependent on the time when the damage occurs.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: U.S. Army Research Office grant W911NF-15-1-0432

NIH grant 5R25GM077634-04

Title: The anticholinesterase paraoxon elicits presynaptic decline in the dendritic field of hippocampal slices in correspondence with enhanced levels of astrocytic processes and β1 integrin response

Authors: *K. G. FARIZATTO, M. F. ALMEIDA, H. W. ROMINE, K. RENTSCHLER, B. A. BAHR
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Abstract: Anticholinesterase toxins include dangerous nerve agents (e.g. soman) that produce seizures, convulsions, memory deficits, and neuronal loss. The hippocampus is particularly vulnerable, with hippocampal slices also exhibiting synaptic and cytoskeletal vulnerability after low-level soman exposure (Munirathinam & Bahr 2004 J Neurosci Res 77:739). How anticholinesterases affect synaptic integrity is important since evidence indicates post-insult repair responses are mediated through synaptic signaling (Bahr et al. 2002 Exp Neurol 174:37). Here, the toxic anticholinesterase paraoxon (Pxn) was applied to rat hippocampal slice cultures to determine if changes in synaptic composition occur and whether such changes are associated with reactive astrocytes. An acute, high-dose Pxn insult (200 μM) resulted in distinct presynaptic vulnerability after 24 h, evident by a 64% reduction in synapsin IIb immunoblot levels ($p<0.001$) and a similar reduction in synaptophysin. In contrast, the postsynaptic protein GluR1 appeared unaffected by Pxn. Synapsin II tissue staining also exhibited Pxn-mediated decline, a 73% loss of punctate labeling area in the dendritic field of the dentate's molecular layer ($p=0.025$). In the same dendritic view-fields, staining for the specific astrocyte marker GFAP increased significantly. The staining area for astrocytic processes increased 87% in the molecular layer, and the extent of this increase correlated with the extent of reduced dendritic staining of synapsin II in double-labeled confocal images ($R=0.746$, $p=0.033$). Astrogliosis often leads to the generation of harmful free-radicals. Relatedly, the Pxn-treated slice samples were found to exhibit i) more GFAP isoforms than control samples, ii) increased levels of lipocalin-2, a marker of reactive astrocytes, and iii) labeling of the oxidative stress-related 4-HNE marker. The latter was in the form of stable 4-HNE-protein adducts, and they were also found to be released into the culture medium of Pxn-treated slices. Lastly, Pxn caused a nearly two-fold increase in the β1 integrin level, and integrins are known to regulate synapses and the dynamics of the synaptic

environment (see Park & Goda 2016 Nat Rev Neurosci 17:745). These data indicate that Pxn induces distinct synaptotoxicity in combination with a pathogenic cascade involving disruption of cellular homeostasis. They also may shed light on astrocyte-neuron interactions at play during toxin responses in the brain. This work was supported by the U.S. Army Research Office under grant W911NF-15-1-0432, and partly by NIH grant 5R25GM077634-04.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.13/R7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG028383

Title: Vascular risks in older adults are correlated with brainwave patterns of learning and memory

Authors: E. BEDINGAR[1], L. S. BROSTER[1], E. L. ABNER[2], X. ZHAO[3], J. LI[4], G. A. JICHA[2], R. KRYSCIO[2], F. A. SCHMITT[2], C. D. SMITH[2], D. M. WILCOCK[2], *Y. JIANG[1]
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Abstract: BACKGROUND. Vascular cognitive impairment (VCI) is considered the second most common cause of dementia after Alzheimer’s disease. Currently there is limited understanding on Cerebrovascular disease (CVD) risk and neural correlates of cognitive functions. Using Electroencephalography (EEG) and Cognitive Event-related potentials (ERP), we tested the hypothesis that vascular risk factors are associated with alteration of neural mechanisms underlying short-term memory (explicit working memory & implicit repetition learning).
METHODS. 19 older adults (mean age 75.3) from the community-based aging cohort, Univ. of Kentucky Alzheimer’s Disease Center were included in the study. The Framingham 10-Year Risk Percentage and Hachinski Ischemic Score (HIS) for stroke were used to estimate CVD risk of an individual. Systolic Blood Pressure (BPSYS) was used as a proxy to the extent of small vessel disease. Scalp EEG during resting and cognitive ERP during working memory retrieval and repetition at 14 electrode sites were tested. We further conducted a robust regression which accounted for potential effect of an outlier.
RESULTS. We found that Framingham 10-year risk scores were negatively correlated with ERP patterns indexing better working memory [1] at the left frontal sites ($p=0.02 \sim 0.04$). Other sites

did not show significant correlations. Also, HIS and BPSYS did not correlate with the Left frontal ERP, nor machine learning based EEG markers during resting state. In contrast, BPSYS was positively correlated with the right frontal (F4) neural repetition during retrieval of targets (p=0.02) and non-targets (p=0.03). The 10-year Framingham risk and the repeated match and non-match (p=0.04). Also, BPSYS was positively correlated with the neural repetition (i.e. enhanced repetition learning as BPSYS increased). HIS did not show any correlation. CONCLUSIONS. The present results revealed that the left-frontal cognitive ERP (working memory related brainwave patterns) were correlated with the 10-year risk percentage, but not HIS. Additionally, BPSYS was correlated with neural repetition at the bilateral frontal during implicit learning. Our results suggest that various vascular risk factors reflecting stroke or small vessel disease in older adults are associated with different types of short-term memory.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.14/R8

Topic: C.01. Brain Wellness and Aging

Support: USDA ARS

Title: *In vitro* effects of Epidiferphane on adult human neural progenitor cells

Authors: *T. ZHENG[1], D. F. BIELINSKI[1], D. R. FISHER[1], B. SHUKITT-HALE[1], B. A. REYNOLDS[2], D. A. STEINDLER[1]
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Abstract: Neural stem cells have the capacity to respond to their environment, migrate to the injury site and generate functional cell types, and thus they hold great promise for cell therapies. In addition to representing a source for central nervous system (CNS) repair, neural stem and progenitor cells also show great promise for drug screening and toxicity testing. We propose that human neural stem/progenitor cells can also be utilized as a reliable *in vitro* bioassay model for testing, in addition to standard of care and emerging therapies, diet and nutrient components that have potential beneficial bioactions on both the developing and aging human CNS. Adult human neural progenitor cells (AHNPs) isolated and characterized previously in our lab, demonstrate impressive ability to generate diverse neuronal populations. They are used here as an *in vitro* model for testing the effects of Epidiferphane™ (EDP) on progenitor cell's viability,

proliferation and differentiation. EDP is a combination of phytochemicals incorporating green tea catechin epigallocatechin gallate, “EGCG”, the polyphenol curcumin from turmeric, and the isothiocyanate sulforaphane from broccoli sprouts. These nutrient components, together constituting a polymolecular botanical drug, are non-toxic and have demonstrated anti-cancer, anti-inflammatory as well as anti-oxidant properties.
AHNPs were cultured in uncoated plastic dishes in N2 medium supplemented with 5% fetal bovine serum, bovine pituitary extract and growth factors. They were then treated with various doses of EGCG, curcumin and broccoli sprouts, either separately or in combination for 4 days. The viability of the treated cells was examined using the Trypan Blue exclusion method, and proliferation of these cells was evaluated using the ethynyl-deoxyuridine (EdU) assay. A subset of treated cells was labeled with a battery of neuronal markers to examine the differentiation of these cells. To determine whether EDP or its individual compounds could protect AHNPs from stress induced by dopamine (DA) present in the media, some pre-treated cells were exposed to DA for 2 hours and their viability, proliferation as well as calcium buffering were then examined.
While EDP as well as its individual components did not show significant effects on the viability, proliferation and differentiation of AHNPs, they did demonstrate neuroprotection for the AHNPs following cellular stress induced by DA. The data also supports the notion that synergetic effects from the whole compound appear to be more protective when compared to each of the individual components in this human neural progenitor cell bioassay. Supported by the USDA ARS.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.15/R9

Topic: C.01. Brain Wellness and Aging

Support: USDA Intramural

Title: Blueberry and Epidiferphane (EDP) enhance calcium buffering in rat hippocampal cells and reduce stress signalling in microglial cells

Authors: D. R. FISHER, T. ZHENG, D. F. BIELINSKI, D. A. STEINDLER, *B. SHUKITT-HALE
USDA, ARS, USDA-ARS Human Nutr. Res. Ctr. on Aging, Boston, MA

Abstract: Age-related decrements are thought to result from increased susceptibility to and accumulating effects of oxidative stress and inflammation. Some foods and food compounds contain bioactive phytochemicals that exhibit potent antioxidant and anti-inflammatory activities, and these foods have been shown to mitigate cognitive decline in aged animals and humans, perhaps by increasing neurogenesis. At least part of the loss of cognitive function in aging may be dependent upon a dysregulation in Ca^{2+} homeostasis, and this loss affects numerous signaling pathways. This study examined whether the polyphenolics from blueberries or Epidiferphane™ (EDP), a combination of phytochemicals incorporating green tea catechin (epigallocatechin gallate, EGCG), curcumin from turmeric, and broccoli sprouts which contain the isothiocyanate sulforaphane, could enhance calcium buffering in neurons and/or reduce stress signalling in microglial cells. Therefore, rat hippocampal neurons or HAPI microglial cells were pre-treated for a week with various concentrations of either freeze-dried blueberry (BB) extract, EDP, or its individual components before inducing deficits in Ca^{2+} buffering with dopamine (DA, 0.1uM for 2 hours) or inflammation using lipopolysaccharide (LPS, 100 ng/ml overnight), respectively. Results showed that BB and EDP were able to protect against deficits in Ca^{2+} buffering (both % of cells that recovered and time to recovery, $p < 0.05$) induced by DA, showing that pre-treatment with these compounds can reduce both stress- and inflammatory- induced neuronal dysfunction. Additionally, BB and EDP reduced ($p < 0.05$) stress-mediated signalling in HAPI rat microglial cells by attenuating LPS-induced nitrite release, iNOS expression, TNF-alpha release, and COX-2 expression. The individual components of EDP were not as effective as the whole compound, showing that the individual polyphenols in the different components may be acting synergistically or exerting their effects through different and/or independent mechanisms. Therefore, dietary intervention with compounds such as those found in blueberry, green tea, turmeric, or broccoli sprouts can play a role in reducing the age-related central nervous system inflammation, microglial activation, and stimulation of immune pathways that reduce neurogenesis and impair cognitive function.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

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Topic: C.01. Brain Wellness and Aging

Support: USDA Agricultural Research Service

US Highbush Blueberry Council

California Strawberry Commission

Tufts University

Title: Berry phenolics are associated with cognitive enhancement in blueberry- and strawberry-supplemented healthy older adults

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Abstract: The aging process often involves functional declines in cognition, leading to lower quality of life and increased need for care among older adults. Epidemiological evidence suggests that a diet rich in fruits and vegetables can reduce the risk of age-related cognitive impairment, in part due to the presence of antioxidant and anti-inflammatory phytochemicals in these foods, e.g., polyphenols. In recent double-blind, placebo-controlled clinical trials conducted by our laboratory, healthy older adults (ages 60-75) consumed 12 g of freeze-dried blueberry (equivalent to 1/2 cup blueberries) or strawberry (equivalent to 1 cup strawberries) twice daily for 90 days. In both studies, participants in the control groups consumed an equal amount of a seemingly identical, isocaloric placebo powder twice daily. Participants completed a battery of 8 cognitive tests and provided blood samples at baseline, and again following 45 and 90 days of intervention. Participants in the blueberry group showed enhanced executive function as evidenced by significantly fewer repetition errors in the California Verbal Learning test (CVLT-II; $p = 0.031$) and a reduced switch cost on a task-switching test ($p = 0.033$) across study visits, relative to placebo controls. Participants in the strawberry group showed enhanced learning and memory as evidenced by significantly improved probe trial performance in a virtual water maze during the midpoint visit ($p = 0.020$) and improved word recognition in the CVLT ($p = 0.014$). No significant effects were observed on the other tests. Plasma phenol concentrations, including both parent compounds and metabolites, were measured after an overnight fast and 2 hours postprandial at each time point (the standardized meal included supplement or placebo at 45- and 90-day visits). Levels of circulating polyphenolics, including anthocyanins, ellagitannins, and phenolic acids were significantly altered as a result of berry consumption. Results showed that blueberry and strawberry polyphenols were absorbed and extensively metabolized, resulting in the production of various phenolic acid derivatives and their conjugates. Regression analysis showed that changes in circulating levels of specific phenolic compounds were correlated with the observed changes in cognition. Therefore, the addition of easily achievable quantities of berry fruit to the diets of older adults can improve some aspects of cognition, likely due to increased levels of circulating berry phenolics and their metabolites.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.17/S1

Topic: C.01. Brain Wellness and Aging

Support: Center for Nutrition, Learning and Memory (Round 4)

Title: Modulation of cerebral blood perfusion by cocoa flavanols in aged mice

Authors: *A. SNYDER[1,2], C. KONOPKA[2,1], H. PINARDO[2,1], T. K. BHATTACHARYA[2,1], C. MOULTON[3,4], W. DOBRUCKI[2,1], J. S. RHODES[2,3,1], C. RENDEIRO[2,3,1]
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Abstract: Cocoa-derived flavanols, and in particular (-)-epicatechin, have been extensively shown to exert beneficial effects on vascular function in humans. More recently, there has been a growing interest in understanding to what extent such beneficial vascular effects in the periphery might benefit the central nervous system and further impact cognitive function, particularly in aging. In the present study, we examined the long-term impact (6 months) of oral supplementation with either i) cocoa-flavanols (containing (+)-catechin, (-)-epicatechin and procyanidins) or ii) pure (-)-epicatechin (both delivering a total of 948 ug of flav/g food) on cerebral blood perfusion as assessed by 99m-Tc-HMPAO Single Photon Emission Computed Tomography (SPECT), in an aged mice model (16 to 22 months old). Preliminary data suggests that long-term chronic supplementation (6 months) with cocoa is more effective at maintaining cerebral blood perfusion in aging (parallel design, n=8; age x treatment effect: p=0.019), than pure (-) -epicatechin when delivered at equivalent doses. We are currently examining the effects of the dietary interventions on specific regions across the brain to identify the areas which were significantly affected by flavanol supplementation. Furthermore, we have observed that changes in blood perfusion are unlikely to be mediated by increases in density of blood vessels, as shown by our preliminary data depicting no differences in density of blood vessels across the hippocampal formation. Collectively, these data support a positive modulation of cerebral blood perfusion by cocoa flavanols and may have the potential to counteract age-associated decreases in brain health and cognition.

Disclosures: A. Snyder: None. **C. Konopka:** None. **H. Pinardo:** None. **T.K. Bhattacharya:** None. **C. Moulton:** None. **W. Dobrucki:** None. **J.S. Rhodes:** None. **C. Rendeiro:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.18/S2

Topic: C.01. Brain Wellness and Aging

Title: Comprehensive longitudinal evaluation of aging-related phenotypes of frailty, neurosensory, motor, and cognitive measures in C57BL/6J mice

Authors: T. L. GREEN, T. MCGARR, S. S. WINTER, *L. ANDERSON, S. J. SUKOFF RIZZO
Mouse Neurobehavioral Phenotyping Facility, The Jackson Lab., Bar Harbor, ME

Abstract: The relationship of biological age and chronological age as measures of health span and lifespan vary amongst individuals. Several studies in mice have aimed to identify the most translational measures that best reflect healthy aging and have mainly been limited to physiological assessments that do not include behavioral measures relevant to neurodegeneration. The present studies aimed to evaluate aging mice through a comprehensive, non-invasive behavioral testing battery which included assessments of motor and fine motor function, vision, hearing, short term and working memory, strength, motor coordination and frailty which could be employed longitudinally over the course of an individuals' life span. As expected, male and female C57BL/6J mice (n=8-13 per sex per age) demonstrated aging-dependent increases in a composite frailty index score in line with previous reports for healthy aging mice (Whitehead et al., 2014 J Gerontol A Biol Sci Med Sci) which was inversely correlated with an aging-dependent reduction in core body temperature. In the open field test, male and female C57BL/6J mice demonstrated aging-dependent reductions in distance traveled and rearing activity as well as aging-dependent reductions in spontaneous homecage wheel running consistent with aging related motor impairments. Aging-dependent changes were also observed for visual acuity and acoustic startle responses indicative of aging-related deficits in vision and hearing, respectively. Cognitive assessments of hippocampal spatial working memory in the spontaneous alternation task and short term memory in a novel spatial recognition task also revealed aging-dependent reductions, while interestingly anxiety-like behaviors were decreased with age. Taken together the present studies demonstrate the sensitivity of these behavioral measures to detect aging-related changes in healthy aging C57BL/6J mice and demonstrate the utility of this non-invasive, comprehensive behavioral testing battery for longitudinal assessments across the lifespan of individual mice that could further be employed to study the potential of therapeutic interventions to attenuate the progression of aging related impairments.

Disclosures: **T.L. Green:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **T. McGarr:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **S.S. Winter:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **L. Anderson:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **S.J. Sukoff Rizzo:** A. Employment/Salary (full or part-time):; The Jackson Laboratory.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.19/S3

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Fondation d'Entreprise Michelin

Title: Thrombospondin repeat-derived peptide (NX210): Antioxidative and neuroprotective properties

Authors: *N. DELÉTAGE[1], M. CHALUS[2], A. BOILEAU[2], S. GOBRON[1], L. SAKKA[2]
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Abstract: Oxidative stress is a major, contributing factor to the pathogenesis of traumatic and degenerative affections of the central nervous system (CNS). Oxidative stress arises from a disturbed redox system homeostasis that generates free radicals, activates kinase cascade and finally leads to apoptotic cell death. Neural cells are particularly sensitive to oxidative damages in relation to a relative scarcity in antioxidant compounds and a high level of poly-unsaturated fatty acid that gives them a high susceptibility to lipoperoxidation. Thus, stimulating antioxidant capacities of the neural cells appears as important strategy in the prevention of secondary damage after traumatic injury of the CNS. NX210 is a peptide derived from a thrombospondin type 1 repeat sequence of SCO-spondin, a protein of the extracellular matrix naturally secreted by the CNS during embryogenesis. NX210 was previously shown to increase neurite outgrowth and fasciculation and to inhibit apoptotic cell death. Here we demonstrate the neuroprotective effect of NX210 in several stress conditions on 2 rat cellular models: a B104 neuroblastoma cell line and primary cortical neurons. Treatment with NX210 at 80, 190 and 380 µM in presence of H_2O_2 significantly enhanced B104 cell viability in a dose dependent manner (respectively 39 %, 71% and 94% of viable cells) as compared to B104 cells exposed to H_2O_2 alone (13% of viable cells). We demonstrate NX210 neuroprotective effect was not mediated by β1 integrin, a receptor involved in NX210 neuroregenerative properties. We demonstrate NX210 might reverse the H_2O_2-induced oxidative through an activation of PI3K/Akt and MAPK/ERK signaling pathways. NX210 might modulate the action of various enzymes involved in the redox regulatory system. The protection against oxidative stress was confirmed on primary cortical

neurons exposed to H_2O_2 with a 4-fold increase of cell viability at 380 µM. NX210 did not exert protection against glutamate-induced cytotoxicity on this model. In conclusion, NX210 combines neuroregenerative properties with antioxidative and antiapoptotic properties that suggest NX210 as a promising candidate to be investigated in traumatic and degenerative affections of the CNS.

Disclosures: **N. Delétage:** A. Employment/Salary (full or part-time):; Neuronax. **M. Chalus:** None. **A. Boileau:** None. **S. Gobron:** A. Employment/Salary (full or part-time):; Neuronax. **L. Sakka:** 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.; Neuronax.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.20/S4

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: The individual and multiple effects of Caulis Spatholobi, Salvia officinalis and Mentha citrate in hydrogen peroxide-induced neurotoxicity

Authors: *K. SUEN[1], T. H. LEE[1], Y. Y. CHEUNG[1], C. K. CHEUNG[1], K. C. WONG[1], S. T. CHAN[1], C. Y. LAW[1], C. L. CHAU[1], S. W. WONG[1], C. C. MOK[1], W. Y. TSUI[1], K. Y. WAN[1], J. S. WONG[1], T. H. HSU[1], W. S. TANG[1], M. Y. LIN[1], R. C. CHANG[2]
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Abstract: Traditional Chinese medicine is usually formulated as a complex of herbs which may have synergistic effects for a disease. Sometimes, the overwhelming effect from a particular herb can be alleviated by antagonistic herbs. Therefore, mixtures of herbal ingredients may have advantages of multiple target regulation. *Caulis Spatholobi*, a commonly used herbal medicine for blood-activating and stasis-dispelling, has been reported to promote angiogenesis. Leaf and root extracts of *Salvia officinalis* (Common name: Sage) have been shown to have antiproliferative effects on hepatocellular carcinoma cells. *Mentha citrate* has been found to have antioxidative effects. In the present study, the individual and multiple effects of *Caulis Spatholobi* extract, seed extract of *Salvia officinalis* and leaf extract of *Mentha citrate* against hydrogen peroxide-induced neuronal cell death were studied. The extracts were prepared by dissolving the powder of ground *Caulis Spatholobi*, fresh sage seed and fresh Mentha's leaves in ethanol and insolubles were filtered out by 0.22 micro-meter membrane filter. Non-differentiated SH-SY5Y cells were pre-treated with a single or multiple extracts for 24 hours in DMEM supplemented with 2% fetal bovine serum. Following the removal of the extracts, SH-SY5Y cells were treated with 400 micro-molar of hydrogen peroxide for 24 hours in DMEM with 2%

fetal bovine serum. Results indicated that there were differential effects of the extracts against hydrogen-peroxide induced cytotoxicity. This implies that some of the extracts may offer neuroprotection.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.21/T1

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: G-protein coupled receptor 110 in synaptamide-induced optic nerve regeneration and improvement of visual function after optic nerve damage

Authors: *H. KWON, T. PARK, H.-Y. KIM
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Abstract: The adult mammalian central nervous system (CNS) has a very limited ability to regenerate axons, and therefore, axonal damage often leads to irreversible functional deficits. Synaptamide (*N*-docosahexaenoylethanolamine), a structural analog of the endocannabinoid anandamide, is produced endogenously from an omega-3 fatty acid docosahexaenoic acid (DHA). We have previously demonstrated that synaptamide promotes neurite outgrowth and synaptogenesis in developing neurons *in vitro* as well as *in vivo* by binding to G-protein coupled receptor 110 (GPR110, ADGRF1) the expression of which becomes negligible in the brain after development except for the hippocampus. We have also observed using an *in vitro* axonal injury model that synaptamide at10 nM significantly promotes axon regrowth in developing cortical neurons. In this study, we demonstrate that synaptamide induces axon regeneration in adult mice after optic nerve injury in a GPR110-dependent manner, resulting in improved visual activity. To test the axon regeneration by synaptamide *in vivo*, we performed optic nerve crush (ONC) followed by an intravitreal injection of synaptamide (25 mg/kg) and the optic nerve tissues were collected after 4 weeks after injury. Optic nerve visualization performed by the intravitreal injection of a fluorescent anterograde tracer cholera toxin B subunit (CTB) at 3 days before the tissue collection indicated that synaptamide but not oleoylethanolamide strongly promoted axon regeneration; however, such synaptamide effect was not observed in *gpr110 KO* mice. Moreover, the visual function evaluated at 12 weeks after injury by the electroretinogram (ERG) and visual evoked potential (VEP) was restored by the single injection of synaptamide following ONC in wild type but not *gpr110 KO* mice. When the CTB-stained retinal ganglion cell

projection to the brain was examined at 12 weeks after injury, the retinal fiber innervation was detected in mice treated with synaptamide while no such innervation was apparent in vehicle treated animals. Significant and persistent induction of *gpr110* in retina was observed by *in situ* hybridization and qRT-PCR in as little as 30 min post injury, indicating that *gpr110* is not only a developmental gene but also an injury-responding gene that facilitates the repair. Taken together, these findings suggest that the synaptamide/GPR110 signaling is a potential therapeutic target for functional recovery after CNS injury such as optic nerve or spinal cord injury.

Disclosures: H. Kwon: None. **T. Park:** None. **H. Kim:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.22/T2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Weston Brain Institute

Title: Therapeutic targets in vascular cognitive impairment and dementia: Neuroinflammation and endothelial dysfunction

Authors: *D. J. BRAUN, A. BACHSTETTER, D. GOULDING, D. WILCOCK, L. VAN ELDIK
Univ. of Kentucky, Lexington, KY

Abstract: Vascular cognitive impairment and dementia (VCID) is recognized as the second leading cause of dementia behind Alzheimer’s disease (AD). Although a distinct clinical entity from AD, VCID has many similar pathological dysfunctions and risk factors. Pathogenic mechanisms responsible for VCID are diverse and overlapping, however two major contributors can be broadly identified: dysregulated inflammatory processes, and endothelial dysfunction. Hyperhomocysteinemia (HHcy) is defined by elevated plasma homocysteine levels, and it is an established risk factor for cardiovascular disease, VCID, and AD. Mice fed a diet deficient in folate, vitamin B6, and vitamin B12, and supplemented with excess methionine, develop HHcy. This corresponds with microhemorrhages, neuroinflammation, and cognitive deficits, and is therefore a useful animal model of VCID. Using this HHcy model, we have explored several potential approaches to ameliorate pathological damage: pharmacological attenuation of glial pro-inflammatory cytokine expression with a highly brain-penetrant small molecule, genetic knockout (KO) of p38α mitogen activated protein kinase (MAPK) from myeloid cells, and reducing permeability of the blood brain barrier by KO of myosin light chain kinase (MLCK) from endothelial cells. Pharmacological inhibition of glial cytokine release did not attenuate pathology. Loss of p38α MAPK, however, reduced neuroinflammatory changes and

microhemorrhage, as did KO of MLCK from endothelial cells. Taken together, our data suggest that targeting peripheral or vascular-associated inflammation, and in particular reducing leukocyte infiltration into the brain, may be a useful approach in ameliorating VCID-associated neuropathology.

Disclosures: D.J. Braun: None. **A. Bachstetter:** None. **D. Goulding:** None. **D. Wilcock:** None. **L. Van Eldik:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.23/T3

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant UL1TR000117

T32 DA016176 (MAS)

Palisades Therapeutics, LLC

Title: Daidzein induces cytoprotection against binge-like ethanol exposure *In vitro:* Role of high mobility group box 1 protein?

Authors: *M. A. SAUNDERS, J. E. JAGIELO-MILLER, M. A. PRENDERGAST
Psychology, Univ. of Kentucky, Lexington, KY

Abstract: An estimated 18 million Americans currently meet criteria for an alcohol use disorder. While there are currently four medications approved by the US Food and Drug Administration to treat AUD: disulfiram, naltrexone, long-acting injectable naltrexone, and acamprosate, these treatments have not been successful, with 50-80% reporting relapse at 1 year follow-up. The lack of efficacy of the current treatments may be attributed to their focus on the motivational behaviors of abuse, rather than the neurobiological effects of alcohol that may underlie those behaviors. Thus, understanding the neurobiological mechanisms which result in the neurological deficits and cognitive decline from chronic alcohol use and withdrawal remains a major goal in the development of effective pharmacotherapies for alcohol use disorder (AUD). Naturally found isoflavonoids, a sub-class of flavonoids, have been demonstrated to reduce ethanol (EtOH) intake in rats and humans. Notably, these compounds are reported to have a myriad of properties (i.e. estrogen receptor binding, anti-inflammatory, antioxidant, cytoprotective). However, the mechanisms by which isoflavonoids attenuate on EtOH consumption it not yet know. The current studies examined the effects of daidzein (0.0001-0.01 µM), a prototypical isoflavonoid which has been demonstrated to attenuate ethanol consumption *in vivo*, on EtOH (100 mM)-induced cytotoxicity in organotypic hippocampal slice cultures. EtOH (100mM) induced

significant cytotoxicity (as measured by propidium iodide [PI] uptake) at 48h. Daidzein was protective against EtOH (100mM) - induced cytotoxicity at all concentrations tested. Follow-up studies were conducted to examine if daidzein exerts its neuroprotective effects through inhibition of neuroinflammation. *High mobility group box 1* protein (HMGB1) interacts with *toll-like receptor 4* (TLR4) receptors, and is considered a pro-inflammatory signal associated with binge EtOH consumption. EtOH (100mM) significantly increased secreted HMGB1 concentrations in culture medium at 48h. Daidzein significantly attenuated this increase at all concentrations tested. These results suggest potential anti-inflammatory properties of daidzein which may contribute to its cytoprotective effects in the presence of EtOH. These findings further highlight the potential applications of daidzein for use in the treatment of AUD.

Disclosures: M.A. Saunders: None. **J.E. Jagielo-Miller:** None. **M.A. Prendergast:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.24/T4

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Pgrmc1 mediates progesterone-induced protection against oxidative stress glial and neuronal cells

Authors: *S. KIM, T. NGUYEN, J. TOOFAN, N. RYBALCHENKO, M. SINGH
Ctr. for Neurosci. Discovery, Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX

Abstract: Our laboratory has previously reported that Brain-derived neurotrophic factor (BDNF) is a critical mediator of progesterone's (PROG) cytoprotective effects on brain cells. And though the effects of PROG on BDNF expression (mRNA and protein) are regulated by the classical progesterone receptor (PR), our lab has identified Pgrmc1 as a novel receptor for PROG that mediates BDNF release from glia. Accordingly, we hypothesized that Pgrmc1 plays an equally important role in mediating the protective effects of PROG in both astrocytes and neurons, given the recognized importance of BDNF on both neurons and glia. Using C6 astrocytes and differentiated SH-SY5Y neuronal cells, we found that PROG protects both cells from the pro-oxidative insult, H_2O_2. Interestingly, this effect was independent of the classical PR. We then used RNA interference (RNAi)-mediated gene depletion to knock down the expression of Pgrmc1 and determined if PROG-induced BDNF release was attenuated. Pgrmc1 depletion completely abolished the BDNF release elicited by PROG. We also used pharmacological strategies to determine whether the effect of PROG on cell viability (both C6 and SH-SY5Y) was mediated by the classical PR, the 5-alpha reduced metabolite of PROG, Allopregnanolone, or Pgrmc1. While neither the pharmacological inhibitors of the PR and 5-alpha reductase altered the protective effects of PROG against H_2O_2, inhibition of Pgrmc1 prevented PROG from

protecting against this pro-oxidative insult. Further, inhibition of trkB also abolished the PROG protective effect, implicating that the release and subsequent binding of BDNF to its cognate receptor was, at least in part, involved in mediating the protective effects of PROG. The data offered here support our model that Pgrmc1 is critical to progesterone's capacity to elicit the release of BDNF and trigger downstream signaling events that are vital for cell viability.

Disclosures: S. Kim: None. **T. Nguyen:** None. **J. Toofan:** None. **N. Rybalchenko:** None. **M. Singh:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.25/T5

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG051470

NIH Grant HD02528

Title: Effects of long-term forelimb resistance training on neuroprotective proteins in the brains of aged rats

Authors: *J. A. STANFORD[1], K. G. STANFORD[2], R. S. ROGERS[3], B. O'MEARA[2], Y. HONG[2], H. NISHIMUNE[4]
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Abstract: Converging evidence suggests that exercise may protect against a number of age-related conditions, including dementia and motor dysfunction. Improved mitochondrial and bioenergetic function, as well as increased neurotrophic factor expression, likely underlie the beneficial effects of exercise. While preclinical aging studies have focused almost exclusively on aerobic exercise, recent studies report the beneficial effects of resistance exercise in maintaining neuronal integrity. Research into the effects of long-term resistance training on neuroprotective mechanisms in the brain is hampered by limitations in implementing resistance training in animals. The resulting knowledge gap is important given the limitations of implementing aerobic exercise regimens in the elderly. The goal of the study was to determine whether long-term resistance training can increase neuroprotective proteins in key brain regions of aged rats. After being trained to perform a unilateral isometric forelimb resistance task, 18-month-old Sprague-Dawley rats performed the task daily for 6 months. Tissue was harvested from striatum, hippocampus, and other brain regions from strength-trained vs sedentary rats at 24 months of

age. Results will be discussed in relation to neuroprotection against age-related cognitive and motor decline.

Disclosures: J.A. Stanford: None. **K.G. Stanford:** None. **R.S. Rogers:** None. **B. O'Meara:** None. **Y. Hong:** None. **H. Nishimune:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

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Program#/Poster#: 667.26/T6

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: TFFI Innovation Award, Thompson Family Foundation, "Development of neuroprotective agents to prevent vincristine-induced peripheral neuropathy"

TFFI Pilot Award, Thompson Family Foundation, "Cellular Physiology"

Title: Discovery of protective small molecules for the treatment of vincristine-induced peripheral neuropathy

Authors: *I. V. UTKINA-SOSUNOVA, H. LI, C. KARAN, S. PRZEDBORSKI, F. LOTTI
Columbia Univ., New York, NY

Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and dose-limiting side effect in cancer treatment with platinum compounds, taxanes, vinca alkaloids, and proteasome inhibitors. Vincristine, a widely used vinca alkaloid, is unique among cancer chemotherapeutics because in addition to sensory neuropathy, its exposure causes motor deficits that are observed as early as one week after initiation of treatment. However, very little attention is reserved to the mechanisms underlying vincristine-induced motor dysfunction. We are using a pharmacological approach to understand the mechanisms underlying vincristine-induced axonal degeneration in motor neurons and to devise therapeutic strategies to treat or/and prevent vincristine-induced peripheral neuropathy (VIPN). Toward this goal, we developed an automated, an imaging-based assay suitable for 96- and 384- well plate formats to determine motor neuron cell number and neurite length. Using this setup, we tested the effect of several concentrations of vincristine on survival and neurite length of genetically labeled motor neurons derived from mouse embryonic stem cells and found that 24 hours treatment of motor neurons with 2nM of vincristine resulted in a significant and highly reproducible reduction in neurite length without affecting cell survival. To validate the ability of our cell-based assay to identify compounds that protect axons from vincristine-induced degeneration, we screened a library of biologically active small molecules. The reliability of our screening methodology is highlighted by the identification within the hits of compounds whose targets have been previously implicated

in axon degeneration. Thus, we established a consistent and robust cell-based phenotypic assay that accurately measures vincristine-induced effects on neurite length of motor neurons and is amenable to high-throughput chemical and genetic screens.

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Poster

667. Therapeutic Development for Neurodegenerative Diseases

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Topic: C.01. Brain Wellness and Aging

Support: NIH R01 AG050518 to JRF

USC SPARC Grant to CBC

Title: Intranasal orexin-A (hypocretin-1) activates cholinergic and GABAergic neurons in select brain regions of aged animals

Authors: *C. B. CALVA[1], J. R. FADEL[2]
[1]Univ. of South Carolina, Columbia, SC; [2]Pharmacology, Physiology, Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: Hypothalamic orexin/hypocretin (OX) neurons have recently been implicated in coordinating homeostatic and cognitive functions. OX neurons send widespread projections to the cortex and provide robust innervation to all subgroups of the basal forebrain cholinergic system (BFCS). Prior work from our lab has demonstrated an age-related reduction of OX neurons in rats, suggesting that orexins play a role in the cognitive and homeostatic dysfunction seen with age. Intranasal orexin-A (OxA) has been suggested as a novel therapeutic for the treatment of age-related cognitive disorders, including Alzheimer's disease. We have previously demonstrated that intranasal OxA activates cortical and basal forebrain regions involved in attention and learning, and increases cortical acetylcholine and glutamate release. Accordingly, we investigated the effects of intranasal OxA administration in aged animals. Here, aged (26-28 months) male Fisher344/Brown Norway rats received intranasal administration of vehicle (0.9% saline) or OxA (25 ul of a 100uM solution) into each nare. At two hours post-treatment, animals were sacrificed and their brains were processed for immunohistochemical detection of the neuronal activity marker, c-Fos, and phenotypic markers of specific neuronal populations. Intranasal OxA significantly increased c-Fos expression in the prelimbic medial prefrontal cortex (mPFC) and agranular insular cortex (AIC) compared to vehicle treatment. The medial prefrontal (mPFC) and agranular insular cortices (AIC) are involved in attentional and interoceptive

functions, respectively. Interestingly, c-Fos expression in parvalbumin positive (PV+) interneurons was decreased in the mPFC. Intranasal OxA also increased c-Fos expression in PV+ GABAergic neurons of the nucleus basalis/ventral pallidum/substantia innominata (VP/SI/NBM), which tend to form inhibitory synapses onto cortical PV+ GABAergic interneurons. Intranasal OxA also significantly increased activation of cholinergic neurons in both limbs of the diagonal band of broca (DBB) and in the NBM/VP/SI continuum. NBM/VP/SI provides cholinergic innervation to the cortex while the DBB supplies cholinergic innervation to hippocampal regions. Intranasal OxA did not alter c-Fos expression in all cortical and basal forebrain regions, suggesting that intranasal OxA effects are not a global phenomenon. In total, these data demonstrate a capacity for intranasal OxA administration to activate brain regions and neurotransmitter systems that degenerate in aged animals and, therefore, may serve as a viable therapeutic option for treating age-related cognitive disorders.

Disclosures: C.B. Calva: None. **J.R. Fadel:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.28/T8

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Defense Threat Reduction Agency - Joint Science and Technology Office

Title: Upstream genomic analysis for the identification of novel therapeutic candidates for the treatment of chemical warfare nerve agent exposure

Authors: *H. M. HOARD-FRUCHEY[1], T. M. FERRARA-BOWENS[2], J. K. CHANDLER[4], J. IRWIN[3], K. LAITIPAYA[3], D. D. PALMER[5], E. A. JOHNSON[6]
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Abstract: Chemical warfare nerve agents (CWNAs) such as sarin and soman are potent inhibitors of acetylcholinesterase. Inhibition of acetylcholinesterase causes accumulation of acetylcholine, resulting in hypersecretions, convulsions, seizures, and death. Recent events in Syria demonstrate the severe effects of these agents and underscore the need for improved medical countermeasures for treatment of exposure. To facilitate identification of candidate countermeasures for CWNA exposure, genomic analysis was performed on piriform cortex samples from wild-type mice (C57BL/6J) exposed to a convulsive dose of soman (1.6 x LD_{50}). Samples were collected at 1, 3, 6, 12, 24, and 48 hours following soman exposure, and flash

frozen in liquid nitrogen. Total RNA was isolated and processed for hybridization to Affymetrix HT MG-430 PM array plates. After robust multiarray averaging (RMA) for normalization, principal component analysis (PCA) was used to identify major sources of variation in the data. ANOVA (analysis of variance) was then conducted to identify soman-induced changes in gene expression over time (p-value $\leq .05$; fold change ≤ -1.5 or ≥ 1.5). Identified genes were imported into Ingenuity Pathways Analysis software, and upstream analysis was used to identify potential therapeutic compounds. Eleven compounds were observed in the upstream analysis across all time points, with an additional 4 compounds observed for 1 through 24 hours. Upstream analysis at 48 hours resulted in the greatest number of potential therapeutic compounds (97), followed by 12 hours (93) and 6 hours (89). Therapeutics previously identified and evaluated based on known physiological and biochemical effects of soman were also identified including pentobarbital, thalidomide, resveratrol, and anakinra. Down selection of the candidate countermeasures for efficacy testing in animals will be conducted based on the therapeutic window for administration of the compound, mechanism of action of the compound, and known physiological effects of CWNA exposure.
The views expressed in this poster are those of the author(s) and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government. The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011), and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.

Disclosures: H.M. Hoard-Fruchey: None. **T.M. Ferrara-Bowens:** None. **J.K. Chandler:** None. **J. Irwin:** None. **K. Laitipaya:** None. **D.D. Palmer:** None. **E.A. Johnson:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.29/T9

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Proton irradiation and pomegranate supplementation can both increase proliferation of new cells in the mouse brain

Authors: *N. KALYNOVSKA[1], M. DULCICH[2], N. BAJWA[2], D. XU[3], D. BAYLINK[3], R. HARTMAN[2]
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Abstract: Previous research has demonstrated substantial health benefits of dietary polyphenols. These compounds, which are present in a variety of foods (including pomegranates), have demonstrated neuroprotective effects against various types of neuropathology, including Alzheimer's disease and stroke. Additionally, maternal diet can impact future mental health of the developing embryo, and prenatal pomegranate supplementation has been shown to increase resilience to neonatal hypoxic-ischemic brain injury in mice. Irradiation with protons (e.g., radiotherapy for cancer) can induce cognitive and other behavioral deficits in mice, and we recently showed that dietary supplementation with pomegranate juice protected against some of those effects, although the mechanisms were undetermined. We therefore hypothesized that dietary supplementation with pomegranate juice either protected the brain or enhanced its repair following proton irradiation. Mice received pomegranate juice via mothers' intake for 10-16 days prior to birth and after birth via their drinking water. At 13-14 weeks of age, mice were irradiated with 2 Gy proton radiation (1-2 gy/min) and sacrificed 1 week later. Intriguingly, histological analyses implementing Ki-67 and DAPI stains revealed increased numbers of new cells in irradiated and pomegranate-exposed mice, with the greatest numbers of new cells observed in those mice exposed to both.

Disclosures: **N. Kalynovska:** None. **M. Dulcich:** None. **N. Bajwa:** None. **D. Xu:** None. **D. Baylink:** None. **R. Hartman:** None.

Poster

667. Therapeutic Development for Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 667.30/T10

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: CNPq Grant 305810/2014-6

Title: Troxerutin has neuroprotective effect in rodent model of Parkinson's disease

Authors: *G. M. ANDRADE[1], P. C. SOUSA[1], M. R. CARMO[1], J. R. BEZERRA[1], A. A. ALVES[1], I. VIEIRA[2]
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Abstract: Parkinson's disease (PD) is the second most common form of neurodegenerative disease in the elderly. It is characterized by a progressive degeneration of dopaminergic neurons in the substantia nigra. The clinical aspects of PD shows an intersection between motor symptoms, cognitive, behavioral and neuropsychiatric changes. The neurotoxin 6-hydroxydopamine (6-OHDA), leads to destruction of dopaminergic nerve terminals, mimicking behavioral, biochemical, and pathological changes that are typical of PD. Several studies have

been showing that natural products, especially flavonoids, have protective effect in the prevention or treatment of neurodegenerative diseases. The troxerutin, naturally occurring substance, has strong anti-inflammatory activity, with potential neuroprotective action. The aim of this study was to investigate the effects of troxerutin on neurotoxicity induced by 6-OHDA. Male Wistar rats were divided (220-250 g) into four groups: sham-operated (SO), SO + T200 (animals treated with troxerutin 200 mg/kg intragastrically for 18 days), 6-OHDA (animals that received stereotaxic injections of 6-OHDA 18 g/3μl in the right striatum for 18 days), and 6-OHDA +T200 (animals that received stereotaxic injections of 6-OHDA and were treated with troxerutin 200 mg/kg intragastrically for 18 days). Treatment with troxerutin decreased the number of contralateral rotations in the test of apomorphine, improved the early memory of the animals in the passive avoidance test and procedure memory in the cued version of the Morris Water maze. The troxerutin also prevented the microgliosis and astrogliosis in the striatum and decreased the neuro-inflammation by reducing expression of TNF-α, NF-κB p65 and p-Akt in the striatum. These findings reveal the neuroprotective action of troxerutin via attenuation of neuroinflammation, and encourage further investigations on using troxerutin, as a possible preventive and/or adjuvant therapeutic intervention against PD.

Disclosures: G.M. Andrade: None. **P.C. Sousa:** None. **M.R. Carmo:** None. **J.R. Bezerra:** None. **A.A. Alves:** None. **I. Vieira:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 668.01/T11

Topic: C.03. Parkinson’s Disease

Support: Thomas Hartman Foundation for Parkinson Research

Title: Planning and execution deficits of anterior lateral motor cortex and licking in hemi-parkinsonian mice

Authors: *K. CHEN, R. VINCIS, A. FONTANINI
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Abstract: Parkinson’s disease (PD) is characterized by a progressive degeneration of dopaminergic neurons that results in problems with movement initiation and execution. Experimental evidence shows that, in physiological conditions, the motor cortex plays an important role in motor planning, initiation and execution. In rodents, the anterior lateral motor (ALM) cortex has been shown to be responsible for planning and execution of licking. Little is known about the potential dysfunction of ALM circuits in PD-like conditions. Here, we combine electrophysiological recordings, two-photon calcium imaging, behavioral training and

pharmacological manipulations to study how the abnormal neural activity in ALM causes abnormal licking in a mouse model of PD.
6-hydroxydopamine was unilaterally injected into the medial forebrain bundle (MFB) to produce a mouse model of PD. A control group received a MFB injection of vehicle. In order to investigate licking preparation and execution, mice were trained to lick a movable spout to receive sucrose 1 s after an anticipatory auditory cue (tone, 2k Hz, 70dB). In one group of mice, 16-electrode arrays were bilaterally implanted into ALM to record spiking activity from neurons in both hemispheres. In a second group, AAV virus expressing GCaMP6s, a genetically encoded calcium indicator, was injected into ipsilateral ALM and a chronic window was implanted above ALM. Neural activity was recorded through 2-photon microscopy.
Hemi-parkinsonian mice displayed two types of licking deficits. First, licking initiated later and terminated earlier in hemi-parkinsonian mice compared to control mice. Second, tongue protrusions were deviated towards the lesion side. The first symptom was fully recapitulated by local infusion of dopamine D1/D2 receptor blockers (SCH23390 and raclopride) in ALM, suggesting a causal role of dopaminergic signaling in this area for preparatory deficits.
Electrophysiological recordings and calcium imaging in the ALM of control hemispheres revealed that most neurons in ALM changed their firing activity in preparation for licking. The ALM of lesioned hemispheres showed a significant reduction in the number of neurons with inhibitory preparatory responses. Ramping of preparatory activity was also slower in the lesioned hemisphere of hemi-parkinsonian mice compared to controls.
In conclusion, our data show that hemi-parkinsonian mice display problems with licking initiation and execution, some of which directly relate to disruption of dopaminergic signaling in ALM. Neural activity in ALM of hemi-parkinsonian mice shows deficits that are consistent with the behavioral observations.

Disclosures: **K. Chen:** None. **R. Vincis:** None. **A. Fontanini:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 668.02/T12

Topic: C.03. Parkinson’s Disease

Support: Hartman Center for Parkinson's Research

Title: Synaptic transmission onto primary motor cortex neurons in a mouse model of Parkinson's disease

Authors: *O. K. SWANSON[1], A. MAFFEI[2]
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Abstract: Primary motor cortex (M1) is a major output center in the circuit for voluntary movement. M1 receives motor signals from the basal ganglia via a glutamatergic projection from the motor thalamus (VA/VL), integrates these signals with inputs from other motor-related areas, and sends its output to descending motor tracts to drive movement. Despite its crucial role in the motor circuit, little is known about the synaptic physiology of neurons in M1. Furthermore, the loss of dopamine signaling that occurs in Parkinson's Disease (PD) has been shown to alter synaptic transmission in other nodes of the motor circuit, but the role that M1 plays in the pathophysiology of this disease remains unclear. To investigate how diminished dopamine signaling impacts overall synaptic transmission in M1, we performed whole-cell recordings of excitatory M1 neurons in acute slice preparations from mice with unilateral nigral 6-hydroxydopamine (6-OHDA) lesions or vehicle injections. We measured spontaneous excitatory and inhibitory postsynaptic currents by blocking action potentials and recording at the reversal potentials for inhibitory or excitatory events, respectively. Analysis of synaptic currents onto layer 2/3 excitatory neurons in M1 revealed that the balance between excitation and inhibition was shifted toward greater inhibition in 6-OHDA lesioned mice (6-OHDA = 0.377±0.035, Control = 0.530±0.0556; $p < 0.04$). Previous studies have shown that in mouse models of PD, pyramidal neurons in M1 undergo changes in spine dynamics, suggesting that PD affects glutamatergic signaling in this region. In view of these data, we hypothesized that the observed shift in E/I balance may be due to altered glutamatergic transmission onto M1 neurons. We focused on the thalamocortical projection from VA/VL to M1 as this constitutes a major glutamatergic input to this area, and published work suggests that in PD the excitability of neurons in the motor thalamus may be suppressed by increased inhibition from the basal ganglia. We combined nigral 6-OHDA or vehicle injections with optogenetic tools to selectively stimulate VA/VL terminal fields, and measured the magnitude and short-term dynamics of the evoked responses in excitatory M1 neurons. Preliminary data show a trend toward reduced VA/VL-M1 input onto layer 2/3 neurons of lesioned animals (EPSC amplitude (pA), 6-OHDA = 120.509±57.259, Control = 341.897±114.653). Overall, this study will further our understanding of the effects of PD on the circuit in M1, possibly helping to identify more targeted treatment options for this disease.

Disclosures: O.K. Swanson: None. **A. Maffei:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 668.03/U1

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01NS070865

NIH Grant 1R01 NS091853-01

Title: Movement-related activity in the basal ganglia-recipient motor thalamus (VLa) of the parkinsonian macaque

Authors: *D. KASE[1,2], A. J. ZIMNIK[4], T. M. PEARCE[3,2], R. S. TURNER[2]
[1]Dept. of Neurobio., Systems Neurosci. Inst., Pittsburgh, PA; [2]Dept. of Neurobio., [3]Dept. of Pathology, Univ. of Pittsburgh, Pittsburgh, PA; [4]Dept. of Neurosci., Columbia Univ., New York City, NY

Abstract: Disordered function of the VLa thalamus is thought to be a critical step in the pathophysiology of motor impairments in Parkinson's disease (PD). For example, the traditional "rate model" hypothesizes that elevated discharge rates in efferents from the parkinsonian basal ganglia cause excessive inhibition of VLa neurons, which may be evidenced by reduced baseline discharge rates and/or reduced magnitude of movement-related increases in activity. Little information is available, however, on how the activity of VLa neurons is altered in the parkinsonian state. To address this gap in knowledge, we sampled single unit extracellular activities from the VLa before and after (n=99 and 96 units, respectively) the induction of hemiparkinsonism by intracarotid MPTP administration in one macaque monkey. The animal performed a simple choice reaction time reaching task for food reward. The animal was able to perform the task throughout the months-long recording period following MPTP, but with markedly prolonged and more variable reaction times and movement durations (reaction time: 248±35 ms vs. 457±215 ms, movement durations: 244±35 ms vs. 845±333 ms, means±SEM pre- vs. post-MPTP respectively; $p<0.01$ for both K-S test). The baseline firing rates of VLa neurons, sampled during attentive rest while the animal waited for the task's "go" stimulus, were not altered by MPTP (14.0±1.2 Hz pre- vs. 12.0±1.1 Hz post-MPTP respectively; $p>0.05$, K-S test). Large fractions of neurons changed firing rates around the time of reach onset (92% and 83% of neurons pre- and post-MPTP; $p=0.07$ χ^2-test), with increased firing as the earliest change in 79% (pre-MPTP) and 61% (post-MPTP) of these cells, and decreased firing as the earliest change in the remainder. This shift following MPTP toward early movement-related decreases in firing was significant ($p=0.01$; χ^2-test). In addition, the magnitudes of movement-related increases in firing were reduced markedly following MPTP (20.9±2.2 Hz pre- vs. 5.0±0.7 Hz post-MPTP; $p<0.01$ K-S test) whereas the magnitude of decreases did not differ (6.2±0.8 Hz pre- vs. 6.1±1.0 Hz post-MPTP). Finally, peri-movement activity began earlier relative to movement onset following MPTP (96.5±14.2 ms pre- vs. 176.8±19.9 ms post-MPTP respectively; $p<0.01$, K-S test). The shift in timing was similar for increases and decreases in firing. The observed MPTP-induced reductions in the prevalence and magnitude of movement-related increases in activity lend partial support for the traditional rate model of PD pathophysiology.

Disclosures: D. Kase: None. **A.J. Zimnik:** None. **T.M. Pearce:** None. **R.S. Turner:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 668.04/U2

Topic: C.03. Parkinson’s Disease

Support: CIBF Grant CE140100007

Laureate Fellowship Grant FL140100025

Title: Unified neural field theory of brain dynamics underlying oscillations in Parkinson's disease and generalized epilepsies

Authors: *E. J. MULLER[1], S. J. VAN ALBADA[2], J.-W. KIM[1], P. ROBINSON[1]
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Abstract: The mechanisms underlying pathologically synchronized neural oscillations in Parkinson’s disease (PD) and generalized epilepsies are explored in parallel via a physiologically-based neural field model of the corticothalamic-basal ganglia (CTBG) system. The basal ganglia (BG) are approximated as a single effective population and their roles in the modulation of oscillatory dynamics of the corticothalamic (CT) system and vice versa are analyzed. In addition to normal EEG rhythms, enhanced activity around 4 Hz and 20 Hz exists in the model, consistent with the characteristic frequencies observed in PD. These rhythms result from resonances in loops formed between the BG and CT populations, analogous to those that underlie epileptic oscillations in a previous CT model, and which are still present in the combined CTBG system. Dopamine depletion is argued to weaken the dampening of these loop resonances in PD, and network connections then explain the significant coherence observed between BG, thalamic, and cortical population activity around $4-8$ Hz and 20 Hz. Parallels between the afferent and efferent connection sites of the thalamic reticular nucleus (TRN) and BG predicts low dopamine to correspond to a reduced likelihood of tonic-clonic (grand mal) seizures, which agrees with experimental findings. Furthermore, the model predicts an increased likelihood of absence (petit mal) seizure resulting from pathologically low dopamine levels; this agrees with experiments that show an increased likelihood of absence seizures following dopamine depletion. Suppression of absence seizure activity is demonstrated when afferent and efferent BG connections to the CT system are strengthened, which is consistent with other CTBG modeling studies. The BG are demonstrated as having a suppressive effect on activity of the CTBG system near tonic-clonic seizure states and support the reported efficacy of treatments targeting BG circuits. Sleep states of the TRN are also found to suppress pathological PD activity. Overall, the findings demonstrate strong parallels between coherent oscillations in generalized epilepsies and PD, and provide insights into possible comorbidities.

Disclosures: **E.J. Muller:** None. **S.J. Van Albada:** None. **J. Kim:** None. **P. Robinson:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 668.05/U3

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation

Massachusetts Neuroscience Consortium

NIH/NICHD R37 HD028341

Title: Deletion of the striatal matrix and striosome signaling molecules, CalDAG-GEFI and CalDAG-GEFII, mitigates the onset of abnormal motor responses to L-DOPA in a Parkinson's disease model mouse

Authors: *J. R. CRITTENDEN[1], T. KITSUKAWA[3], H. BOWDEN[2], D. E. HOUSMAN[2], A. M. GRAYBIEL[2]
[1]McGovern Inst. for Brain Research, Brain & Cognitive Sci., [2]MIT, Cambridge, MA; [3]Osaka Univ., Suita, Japan

Abstract: In Parkinson's disease, difficulty in initiating voluntary movement is relieved by dopamine replacement therapy with oral L-DOPA (L-3,4-dihydroxyphenylalanine), which is thought to make up for the degeneration of dopamine-containing neurons in the substantia nigra pars compacta (SNc). A complication of this therapy is the occurrence of L-DOPA-induced dyskinesia (LID), which consists of involuntary movements driven in part by striatal projection neurons (SPNs) that signal abnormally because of severe dopamine depletion and unregulated dopamine release from various cellular sources that convert L-DOPA to dopamine. We previously found that expression of two SPN-enriched signaling molecules of the Ras/Rap/ERK signaling cascade, CalDAG-GEFI and CalDAG-GEFII, is oppositely dysregulated in a rat model of LID. CalDAG-GEFII, which is enriched in the striosome compartment of the striatum, exhibits increased expression, whereas expression of CalDAG-GEFI, which is normally enriched in the extra-striosomal matrix, is reduced. CalDAG-GEFII-positive striosomal SPNs make specialized connections ('striosome-dendron bouquets') with a subset of ventral dopamine-producing neurons, potentially corresponding to those that die early in Parkinson's disease. By contrast, CalDAG-GEFI-positive matrix SPNs target the surrounding, non-dopaminergic nigral regions.
Single CalDAG-GEF knockout mice showed normal motor learning, indicating that they are potential therapeutic targets. We crossed single CalDAG-GEF knockout mice to *pitx3*$^{ak/ak}$

Parkinson's disease model mice to test for changes in responsiveness to L-DOPA treatment. Young *pitx3*$^{ak/ak}$ mice have bilateral loss of SNc neurons and show severe hyperactivity in response to repeated L-DOPA treatments. Mice that were double mutants for *pitx3*$^{ak/ak}$ and either *CalDAG-GEFI* or *CalDAG-GEFII* deletion showed relatively reduced hyper-responsiveness to L-DOPA early in the course of treatment, suggesting that the CalDAG-GEFs might be important for the establishment of L-DOPA hyper-responsivity. To test for molecular correlates of this partial rescue, we evaluated the striatal transcriptome, by RNAseq, from *pitx3*$^{ak/ak}$ mice in the early phase of L-DOPA treatment with and without *CalDAG-GEFI/II* deletion. A dopamine-regulating neuropeptide was found to be upregulated in the *pitx3*$^{ak/ak}$ mice but not in the double mutants, suggesting a possible molecular mechanism for how CalDAG-GEF deletion mitigates L-DOPA hyper-responsiveness. Our findings suggest that the striatum-enriched CalDAG-GEF genes are important for the genesis of LID symptoms in models of this debilitating disorder.

Disclosures: J.R. Crittenden: None. **T. Kitsukawa:** None. **H. Bowden:** None. **D.E. Housman:** None. **A.M. Graybiel:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 668.06/U4

Topic: C.03. Parkinson's Disease

Support: NIH 1R01NS095374-01A1

Title: Aberrant corticostriatal plasticity in Parkinsonian motor inhibition

Authors: *M. J. PATEL[1], D. S. MCGEHEE[2], X. ZHUANG[1]
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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease that is characterized by the death of midbrain dopamine neurons and the long-lasting deterioration of motor output. The indirect pathway of the basal ganglia, which is known to suppress movement, is believed to be hyperactive in PD following the loss of dopamine in the striatum. Our laboratory recently reported that motor training in mice with a D2 dopamine receptor blockade results in a long lasting, experience-dependent motor inhibition that persists even after normal dopamine signaling is restored. To examine the mechanisms that underlie this motor inhibition, we measured changes in corticostriatal plasticity in brain slices following the onset of experience-dependent motor inhibition. We found that motor training under D2 receptor blockade results in strengthening of corticostriatal synapses in the indirect pathway. Furthermore, we found that combining optically driven corticostriatal activity with D2 receptor

blockade led to lasting motor impairment in mice. Our data provide support for potential therapeutic approaches that target corticostriatal plasticity for treating PD.

Disclosures: **M.J. Patel:** None. **D.S. McGehee:** None. **X. Zhuang:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 668.07/U5

Topic: C.03. Parkinson's Disease

Title: Origin of rest tremor in parkinson's disease: Oscillations in neuronal signals or feedback-induced instability in the sensorimotor loop?

Authors: *T. HOMAYOUNI[1], V. V. SHAH[2], S. GOYAL[3], H. PALANTHANDALAM-MADAPUSI[4]
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Abstract: Rest tremor is one of the most common and disabling symptoms of Parkinson's disease (PD). The exact neural origin of rest tremor is still not clearly known. There is a good evidence that tremor may have a pathophysiology different from most other Parkinson's disease symptoms. To date, the pathophysiology of rest tremor is not clearly established. Further, rest tremor does not respond well to dopamine replacement therapy compared to other motor symptoms in PD. Understanding the neural origin of parkinsonian rest tremor is important to optimize the existing treatment strategies such as Deep Brain Stimulation or to develop new alternative treatment strategies for rest tremor reduction.There are broadly two categories of theories that are gaining prominence to explain the origin of parkinsonian rest tremor. The first category is the central oscillator theory, which proposes that the rest tremor is a manifestation of oscillatory signals originating from the brain. These could be produced either by a nucleus with spontaneous rhythmicity or by instability in the local (central) feedback loop consisting of neuronal populations or different nuclei and their axonal connections in the brain. The second category is the feedback-induced instability theory which proposes that the rest tremor is a limit-cycle oscillation that occurs due to feedback-induced instability in the sensorimotor loop caused by increased reaction time (delay in sensorimotor loop). We implemented these two categories of theories in a simulation example of a simple control system, and compared the simulated trends with established clinical observations. We found that majority, but not all of the clinically observed trends support the feedback-induced instability theory. So, in order to arrive at a conclusive answer, we suggest some clinical tests inspired by our simulations.

Disclosures: **T. Homayouni:** None. **V.V. Shah:** None. **S. Goyal:** None. **H. Palanthandalam-Madapusi:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Topic: C.03. Parkinson's Disease

Support: NIH grant P50NS091856

Title: Striatal cholinergic interneurons integrate the attentional control of complex movements

Authors: ***A. J. KUCINSKI**, D. BALLOUZ, Y. KIM, M. SARTER
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Abstract: In addition to the disease-characterizing motor symptoms that reflect primarily striatal dopamine loss, Parkinson's disease (PD) is characterized by widespread neurodegenerative processes in non-dopaminergic brain systems, including cholinergic systems projecting to telencephalic and diencephalic regions. Consistent with the functions of forebrain cholinergic systems in attention, PD patients with cholinergic losses have a propensity for falls attributed to impairments in the attentional supervision of balance and movement. Specifically, cholinergic losses are hypothesized to disrupt attentional processing of exteroceptive and interoceptive cues that normally mediate balance and movement, particularly movements across unfamiliar or dynamic surfaces. As a result, such information is not effectively forwarded to striatal circuitry where, in interaction with dopaminergic losses that cause slow and low-vigor movements, movement planning and sequencing are disrupted and lead to falls. We previously developed a rat model of falls caused by partial basal forebrain cholinergic and striatal dopamine losses. Here we tested the hypothesis that silencing of striatal cholinergic interneurons is sufficient to reproduce such fall propensity, suggesting that these neurons integrate interactions between deficient cue import and low-vigor movement. Rats were familiarized with the Michigan Complex Motor Control Task that requires them to traverse increasingly taxing 3-m long beams, including rotating and zig-zag rods in the presence of distractors. Rats then received bilateral infusions of an inhibitory DREADD (AAV-hSyn-DIO-hM4D(Gi) either into the dorsomedial striatal projection field of the prefrontal cortex or the dorsolateral sensorimotor tier of the striatum. Silencing of dorsomedial, but not dorsolateral, striatal interneurons with CNO administration (5 mg/kg; i.p.) fully reproduced the types and frequency of falls caused by dual cholinergic-dopaminergic lesions. To verify the efficacy of the DREADD we demonstrated attenuated striatal acetylcholine release in response to potassium-evoked depolarization (via reverse microdialysis). These findings suggest that striatal cholinergic interneurons integrate the cortical-striatal import of cue information with high-vigor, dopaminergically-mediated

movement. Treatments to attenuate the risk for falls in PD patients therefore may target striatal interneuronal output to benefit movement error detection and enhance the organization and speed of complex movements.
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Disclosures: **A.J. Kucinski:** None. **D. Ballouz:** None. **Y. Kim:** None. **M. Sarter:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

Location: Halls A-C

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Program#/Poster#: 668.09/U7

Topic: C.03. Parkinson's Disease

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NSF GRFP to PK

Title: Effects of neurofeedback control of beta band oscillations in motor cortex on finger tapping in parkinsonian patients

Authors: *P. KHANNA[1], N. C. SWANN[2], P. A. STARR[3], J. M. CARMENA[1]
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Abstract: Parkinsonian patients have been shown to exhibit exaggerated basal ganglia beta power when they are off-medication or off-stimulation suggesting that exaggerated beta oscillations may contribute to their bradykinesia, rigidity, or tremor symptomology. Previous studies have also demonstrated that motor cortical beta oscillations tend to precede those observed in the basal ganglia suggesting that motor cortex (M1) may be driving downstream basal ganglia beta oscillations. One surprising finding then, is that M1 beta power is not affected by medication or stimulation therapies. Here, we seek to test the role of motor cortical beta power levels on motor actions by using a neurofeedback - movement task structure. Patients learn to control their motor cortical beta oscillations in real time by making a cursor on a screen (which reflects current beta state) increase or decrease to reach a specified level depending on trial. After successfully reaching the instructed beta level, patients immediately after execute a six-second finger tapping sequence. This sequential task structure allows investigation of how high and low motor cortical beta states support subsequent movements.
In previous work we show that patients are able to perform neurofeedback above chance-level,

yet do not exhibit significant improvements within a 1-2 hour session. Thus, in this study, patients get 10 days of training in the comfort of their own home so that they can become proficient at performing neurofeedback control. In one patient with multiple systems atrophy (MSA, parkinsonian subtype), we find that the high and and low beta states reached during neurofeedback precede slower and faster finger tapping onset times respectively. This finding suggests that motor cortical beta power does have a role in movement initiation in the parkinsonian state. We also study the dynamics of finger tapping movements following high and low beta states, dynamics of simultaneously recorded STN beta power signals, and improvement in neurofeedback performance over days. This work contributes to our understanding of M1-STN beta frequency range interactions, M1 beta power dynamics with movement, and develops a potentially therapeutic neurofeedback paradigm for training patients to initiate movement more fluidly.

Disclosures: P. Khanna: None. **N.C. Swann:** None. **P.A. Starr:** None. **J.M. Carmena:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01/R37 NS040894

Duke MSTP T32 GM007171

Title: Causality of beta frequency oscillations in bradykinetic/akinetic parkinsonian symptom generation in rats

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Abstract: Substantial correlative evidence links the synchronized, oscillatory neural firing patterns that emerge in Parkinson’s disease (PD) in the “beta” frequency range (13-30Hz) with bradykinesia in PD. However, conflicting evidence exists, and whether these changes in neural firing pattern are causal of motor symptoms in PD remains unclear. We tested the hypothesis that the synchronized beta oscillations that emerge in PD are causal of symptoms of bradykinesia/akinesia. We designed novel patterns of stimulation that mimicked the temporal characteristics of single unit beta bursting activity seen in PD rats and humans. We applied these beta-patterned paradigms along with continuous low and high frequency controls to the subthalamic nucleus (STN) of healthy and levodopa-treated parkinsonian rats. We quantified the degree of unit entrainment in the substantia nigra reticulata (SNr) as a function of pattern and

amplitude by calculation of the excitatory effective pulse fraction (eEPF) (Agnesi et al 2015). The eEPF (range: 0-1) is a ratio of the number of unit firings evoked by a stimulus pulse to the total number of stimulation pulses referenced to the effects of 'virtual' stimulus pulses during a baseline period. We further quantified the increase in SNr unit spectral beta frequency power due to the applied stimulation paradigms. We found that while patterns entrained units equally, beta-patterned paradigms induced significantly more beta frequency activity than continuous low frequency controls. However, we found no deleterious effects on motor performance across a wide battery of validated behavioral tasks including the bar test, open field test, forelimb akinesia test, adjusting steps test, and skilled forelimb reach test. We applied the same methodology in parkinsonian rats to test whether the neural substrate that emerges in parkinsonism would be more susceptible to the effects of the beta-ergic stimulation patterns. We administered levodopa to 6-OHDA lesioned animals to disrupt endogenous beta activity and allow us to separate the effects of our patterns on motor performance from baseline parkinsonian motor performance. However, although most tests were sensitive to hemiparkinsonism induced by unilateral 6-OHDA lesion, we again found no impact of our patterns on motor performance. Our results uncovered no evidence of a causal relationship between beta frequency oscillations and bradykinesia/akinesia in PD.

Disclosures: C. Behrend: None. **D. Schulte:** None. **D. Brocker:** None. **W.M. Grill:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Program#/Poster#: 668.11/U9

Topic: C.03. Parkinson's Disease

Support: MR/M014762/1

MC_UU_12024/1

Title: Transient beta oscillation dynamics in experimental Parkinsonism

Authors: *H. CAGNAN[1,2], N. MALLETT[3,2], P. J. MAGILL[2], P. BROWN[2], A. SHAROTT[2]
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Abstract: There has been a renewed interest in the transient beta dynamics of cortex and subcortical brain regions involved in motor control. The probability and temporal dynamics of these transient oscillations, referred to as beta burst, have been related to motor performance, and Parkinson's disease treatment state. There have been numerous theories regarding the origin of excessive beta oscillations in the motor circuits of the forebrain, attributing this oscillatory state

to (1) subthalamic and pallidal coupling, (2) internal cortical dynamics, and (3) the interaction between subcortical drive modulating the cortex in a laminar specific fashion. Lesioning any part of the motor circuit however has the capability of quenching neural synchrony in the beta frequency band, highlighting the interdependency between the cortico-basal ganglia circuit and oscillations in the beta band. Previous studies explored time-averaged dynamics of the cortico-basal ganglia circuit during Parkinson's disease with respect to control or medicated Parkinsonian state; however, to accurately determine dynamics underlying the Parkinson's disease pathophysiology, it is vital to characterize the transient changes across the motor circuit at the onset, and the offset of a beta burst. In this study, we set out to address the following questions (1) how is the subcortical neural synchrony and spiking activity modulated at the onset, and offset of a beta burst? and (2) which neural dynamics distinguish physiological short duration beta bursts from pathophysiological long duration beta bursts? In 6-OHDA-lesioned rat model of Parkinsonism, cortical beta bursts consist of short transient oscillations that can last for several beta cycles; maximum beta burst duration being on average 413 ± 67 ms (STD). Basal ganglia nuclei, including the striatum, external globus pallidus and subthalamic nucleus, exhibit enhanced background unit activity (BUA) in the beta band, time locked to the onset of a cortical beta burst. Across different epochs, emergence of rhythmic activity in basal ganglia nuclei is temporally correlated; highlighting that sub-cortical beta can emerge only at a fixed phase relationship with respect to cortical neural activity. Crucially, the phase relationship between the sensorimotor cortex and basal ganglia nuclei changes at the onset and termination of a cortical beta burst. Together, these results provide a framework for characterising the transient oscillations across the motor circuit.

Disclosures: H. Cagnan: None. **N. Mallett:** None. **P.J. Magill:** None. **P. Brown:** None. **A. Sharott:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Topic: C.03. Parkinson's Disease

Support: Diputación de Guipuzcoa, DFG11/019

Instituto Carlos III, PI11/02109

Title: Increased impulsivity following progressive nigral degeneration and chronic pramipexole treatment in a rat model of Parkinson's disease

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Abstract: Dopamine agonists (DA) that are widely used to treat motor deficits in patients with Parkinson's disease (PD) are frequently associated with the development of abnormal-impulsive behaviors (AIB). The pathophysiology of AIB is poorly understood and there is a need for reliable animal models. We have analyzed the behavior of parkinsonian (injection of adeno-associated viral vectors (AAV) encoding for A53T mutated hα-syn in the substantia nigra compacta) and control (AAV-GFP expression) rats under chronic treatment with the D2/D3 receptor DA pramipexole (PPX) during 4 weeks, in OFF and ON medication states, using the 5-Choice Serial Reaction Time-Task (5-CSRTT). Before PPX treatment, the dopaminergic lesion increased the premature responses rate (waiting impulsivity) that was further increased with PPX during the 4 weeks of treatment in ON medication state and that was significantly higher than in control rats. A similar pattern of changes was observed in the variables related to attention (reduced accuracy in the responses and increased omissions). Premature response rate before and after treatment (both in ON and OFF medication) were correlated. In turn, premature responses before treatment and in OFF correlated with the striatal dopaminergic depletion (Dopamine transporter (DAT) immunochemistry). No significant changes were observed in OFF medication state in premature responses rate respect to the pretreatment state. The striatal expression of FosB/ΔFosB inversely correlated with the DAT expression and was higher in the lateral region of both striata and in the shell and core of the nucleus accumbens in parkinsonian than in control rats. In conclusion, these results indicate that the dopaminergic lesion is a risk factor to develop abnormal impulsive behaviors in PD under DA treatment and that this model could be a valid tool to investigate the pathophysiology of AIB in PD.

Disclosures: A. Quiroga-Varela: None. **H. Jimenez-Urbieta:** None. **L. Merino-Galan:** None. **T. Rodriguez-Chinchilla:** None. **I. Navalpotro-Gomez:** None. **M. Delgado-Alvarado:** None. **B. Gago:** None. **M. Rodríguez-Oroz:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 668.13/U11

Topic: C.03. Parkinson's Disease

Title: Does the Lempel-Ziv algorithm provide an unbiased measure of neuronal complexity in the subthalamic nucleus of 6-OHDA lesioned rats?

Authors: *A. MANOHAR, *A. MANOHAR, M. J. MARINO
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Abstract: Parkinson's disease (PD) is characterized by a loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), leading to increased striatal activity, increased inhibition of the globus pallidus externa (Gpe) and subsequent disinhibition of the subthalamic nucleus (STN). Neurons in the STN often exhibit a characteristic burst firing pattern in PD patients. Selective lesions of the nigro-striatal pathway in rodents using a neurotoxin, 6-hydroxy dopamine (6-OHDA),produces changes in basal ganglia physiology including burst firing in the STN which mimic the pathophysiology of Parkinson's. This model has been used extensively to both understand disease mechanisms and develop therapeutic interventions. It has been a challenge to objectively quantify aberrant firing patterns of neurons observed in pathological conditions without making prior assumptions. Here we investigate analytical methods that can potentially overcome this by measuring the complexity of neuronal spike trains without any assumptions about the source. Lempel-Ziv complexity has been broadly used for data compression and loss-less transmission of code for many years. More recently, LZ has been applied to measure the complexity of discrete-time physiological signals. We adapted the LZ complexity for binarized spike trains and normalized the value to the maximum complexity that can be obtained using a spike train of given length. Treating the spike train as string consisting of 0s and 1s we form a vocabulary of distinct words encountered in the string leading to a complexity value. We evaluated the differences in complexity of spike trains obtained from STN neurons in a group of naïve rats (N=41 neurons) and a group of 6-OHDA lesioned rats (N=28 neurons). Our results strongly indicate that the estimation of the LZ complexity is inherently tied to the density of 1s (i.e. the firing rate of the neuron). This finding bears significance, both for understanding our results as well as appropriately interpreting results from previous studies.

Disclosures: A. Manohar: None. **M.J. Marino:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Topic: C.03. Parkinson's Disease

Support: FAPESP Grant, nº 2016/06292-1

Contributing Support: Associação Brasil Parkinson

Title: Parkinson's disease does not alter knee and ankle joint threshold for detection of passive movement

Authors: *G. G. GENOVES[1], C. F. CRUZ[1,2], J. A. BARELA[1,3]
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Abstract: Proprioception is an important source of sensory information and the integrity of proprioceptive information is crucial for performing daily activities. People with Parkinson's disease show changes in several daily tasks such as postural instability and locomotion difficulties. Some of these changes due to the Parkinson's disease have been attributed, among other causes, to proprioceptive impairment of the lower limbs. However, there is still a need to assess and, consequently, to farther uncover possible changes in proprioceptive cues due to Parkinson's disease. Therefore, the aim of this study was to evaluate the threshold for knee and ankle passive movement detection in patients with Parkinson's disease. Ten patients with Parkinson's disease (Age 64.3 ± 5.9 years, stages 1 and 2 on the Hoehn & Yahr scale) and ten health elderly (age 64.1 ± 5.9 years) participated in this study, the age and gender were matched. Initially, participants performed a simple computer reaction time test. Afterward, participants were seated with eyes closed in a chair with a lever that, driven by a motor, passively moved (speed of 0.5º/s) the participant's knee or ankle joint in both directions. At initial position, knee and ankle joints were positioned at 90º. Participants were asked to press a switch, as soon as they detected the limb movement, interrupting the movement. Each participant performed three attempts for each direction in the sagittal plane, randomly distributed, totalizing six attempts for each joint (right and left knee, right and left ankle). A motion analysis system (OPTOTRACK Certus) captured the displacement of the emitters in the chair lever. Total displacement was obtained using the initial and the final position of the device lever. Single reaction time was similar between patients with Parkinson's disease and their peers. Similarly, threshold for knee and ankle passive movement detection did not differ between groups. These results suggest that proprioceptive cues coming from the lower limbs are intact in patients with Parkinson's disease and indicate passive motion of the lower limbs as in health older adults. Thus, any possible changes in proprioceptive information coming from the lower limbs in patients with Parkinson's disease are questioned at least for passive positioning.

Disclosures: G.G. Genoves: None. **C.F. Cruz:** None. **J.A. Barela:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Program#/Poster#: 668.15/V1

Topic: C.03. Parkinson's Disease

Support: CONACYT - GRANT 222009

CONACYT - GRANT 660496

Title: Grey matter changes of vervet monkeys after MPTP administration: Voxel-based morphometry analysis

Authors: *G. RAMÍREZ GARCÍA[1,2], C. CASTILLO-HERNANDEZ[3], J. FERNANDEZ-RUIZ[4], A. CAMPOS-ROMO[5,2]
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Abstract: Parkinson´s disease (PD) is a chronic and progressive disorder characterized by a neurodegenerative process resulting in motor and non-motor disturbances. The main histopathological change is dopaminergic neuron death in the substantia nigra pars compacta that results in low dopamine levels in the striatum. However, other brain structures besides the SNc could be affected in PD. Voxel-based morphometry (VBM) is a neuroimaging technique used to analyze the density changes of grey matter (GM) tissue. Using this technique in PD patients it has been shown GM decreases in frontal and parietal cortices, cerebellum, striatum and hippocampus.
In this study, we used 6 vervet monkeys (*Chlorocebus aethiops*). 3 of them were administrated with MPTP at a dosage of 0.5 mg/Kg of weight once per day (im) during 4-5 consecutive days. The others 3 animals conformed the control group. Whole-brain T1-3D images were obtained in a GE Discovery MR750 3T scan. A specific GM population-template was created with T1 images to make a VBM analysis. The images where analyzed using VBM-FSL tool. Images were reoriented and the inhomogeneities were corrected with FAST-FSL. Brain extraction tool was used to remove the skull from an image. The resulting image was registered to the specific GM template with FNIRT, then a specific template was created and each image was non-linearly registered to the new template and concatenated into a GM 4D template. A second non-linear registration was made between each GM image and a specific GM template was created. The resulting image was multiplied by the Jacobian of the warp field to modulate. Each image was concatenate into a 4D image. Finally, randomize for the TFCE-based analysis between groups was carried out and was corrected by permutation test. The threshold applied was a t value of 2.3 corrected a $p = 0.05$.
The results show GM decrease in the cerebellum, caudate, putamen, thalamus and orbitofrontal, prefrontal, cingulate, temporal and visual cortices. It has been suggested that both striatal and cerebellar changes would be related to the motor alteration, while GM changes in prefrontal and temporo-parietal cortex would reflect cognitive damage. It is known, that PD patients present neurodegeneration in different neuronal systems. In our model, these neuronal damages are reproduced by MPTP administration, for that reason, this neurotoxin represents an excellent way to reproduce the mainly characteristics of PD. These results show that MPTP lesion induces a GM decrement in brain regions related with motor and cognitive process as occurs in PD. Thus,

MPTP vervet monkey is a suitable animal model, useful for neuroimaging studies to evaluate the brain changes in PD.

Disclosures: G. Ramírez García: None. **C. Castillo-Hernandez:** None. **J. Fernandez-Ruiz:** None. **A. Campos-Romo:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Program#/Poster#: 668.16/V2

Topic: C.03. Parkinson's Disease

Support: NS045962

Title: Reduction of SPN firing by NMDAR blockade or DREADDs activation normalizes motor responses to dopamine in animal models of Parkinson's disease

Authors: *G. BECK[1], A. SINGH[2], P. CHANG[2], D. KANG[2], S. M. PAPA[2,3]
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Abstract: Dopamine replacement is an effective treatment for motor dysfunction of Parkinson's disease (PD). However, long-term dopaminergic therapy is associated with changes in motor responses and the development of involuntary movements known as L-Dopa-induced dyskinesia (LID). Studies in rodent and nonhuman primate (NHP) models, as well as in patients with PD, have shown that striatal projection neurons (SPNs) are hyperactive at the baseline parkinsonian state ("off" state). These neurons respond to dopaminergic stimulation with unstable firing changes at the peak of the response, which are associated with the expression of LID. This study was aimed at examining whether decreasing the baseline SPN firing rates towards the low activity found in normal conditions would reduce LID. The SPN activity was reduced "acutely" using local NMDAR blockade in NHP. A selective NMDAR antagonist (LY235959) was infused into one side of the putamen of advanced parkinsonian NHPs (n=3). In addition, the SPN activity was reduced "chronically" by expressing inhibitory DREADDs (designer receptor exclusively activated by designer drugs), hM4Di, in hemiparkinsonian rats. hM4Di is an engineered version of the M4 muscarinic receptor selectively activated by clozapine-N-oxide (CNO), which leads to hyperpolarization in neurons. We injected rAAV-hSyn-hM4D(Gi)-mCherry or the control virus rAAV-hSyn-GFP into the left striatum of rats with 6-hydroxydopamine lesions of the left medial forebrain bundle (n=9). The whole motor response and LID or AIMs (abnormal involuntary movements) were assessed using standardized rating scales for primates and rodents. Results showed that the striatal injection of NMDAR antagonist in the "off" state of NHP significantly reduced LID scores on the contralateral side without

affecting the antiparkinsonian action of L-Dopa acutely. Also, activation of inhibitory DREADDs in rats significantly reduced AIMs during the chronic testing period of two weeks with daily treatment of L-dopa plus CNO. Virus transduction in the rat striatum was confirmed with histological examination. These results indicate that therapeutic strategies to reduce the hyperactivity of SPNs may help to control dyskinesias and improve motor responses to dopamine in patients with PD.

Disclosures: G. Beck: None. **A. Singh:** None. **P. Chang:** None. **D. Kang:** None. **S.M. Papa:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Swedish Research Council

Swedish Parkinson Foundation

Swedish Brain Foundation

New York Stem Cell Foundation

Title: 3D mapping of circuitry integration of transplanted human embryonic stem cell derived neurons in the adult rat brain

Authors: *B. MATTSSON, T. CARDOSO, D. HOBAN, A. HEUER, S. NOLBRANT, A. KIRKEBY, S. GREALISH, M. PARMAR
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Abstract: We have developed a monosynaptic tracing technique to map circuitry integration of transplanted hESCs (Grealish et al., Stem cell Reports). This technique allows for histology-based analysis of host-to-graft connectivity. With this technique, we have developed quantitative and qualitative methods for whole brain mapping/representation of connectivity in 3D-reconstruction and combined that with assessment of graft innervation. Fiber outgrowth from the transplant is outlined in serial sections based on hNCAM stainings and displayed as a volume in a 3D brain reconstructed from Paxinos brain atlas. With the same technique, the traced cells

detected by mCherry are placed in the 3D brain map and each connecting structure is color coded according to a heat map to show the nuclei containing the highest concentration of host cells connecting to the graft. Using this method we have mapped the circuitry integration of midbrain patterned cells transplanted to the midbrain 6 weeks and 6 months after grafting. Analysis of innervation showed that the grafted cells innervated the forebrain target structures after 6 months. Analysis of connectivity revealed that the transplanted cells are integrated with host neurons already by 6 weeks with only minor changes at the 6 month time point. In summary, rabies based tracing combined with 3D re-construction is a valuable method for better understanding kinetics and patterns of graft innervation and integration.

Disclosures: B. Mattsson: None. **T. Cardoso:** None. **D. Hoban:** None. **A. Heuer:** None. **S. Nolbrant:** None. **A. Kirkeby:** None. **S. Grealish:** None. **M. Parmar:** None.

Poster

668. Parkinson's Disease: Circuit Mechanisms

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Swedish Parkinson Fundation

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New York Stem Cell Foundation

Title: Synaptic integration of intrastriatal versus intranigral grafts of human embryonic stem cell derived neurons in the adult rat brain

Authors: *T. CARDOSO, D. HOBAN, B. MATTSSON, A. HEUER, S. NOLBRANT, A. KIRKEBY, S. GREALISH, M. PARMAR
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Abstract: Human embryonic stem cell (hESC)-derived neurons survive long-term, release dopamine and extensively innervate correct host structures after transplantation into adult rat brain. Using the monosynaptic tracing technique, we have recently shown that hESC-derived neurons integrate into host circuitry, establishing both host-to-graft and graft-to-host synaptic

connectivity (Grealish et al., 2015, Stem Cell Reports). Here we use the same methodology to investigate connectivity of midbrain (MB) and forebrain (FB) patterned hESCs-derived neurons transplanted either to striatum or substantia nigra of 6-OHDA lesioned rats. To assess for synaptic connectivity, animals were injected with rabies vector 23 weeks after transplantation and perfused one week later. Analysis 24 weeks post-grafting revealed that host neurons established extensive local and distal synaptic connections with both intrastriatal and intranigral grafts. Connectivity varied more depending on the location of transplantation than the phenotype of the cells grafted. For example, intranigral grafts received more inputs from hypothalamus and intrastriatal grafts received more input from thalamus. In summary, we show that intrastriatal and intranigral grafts of hESC-derived neurons can integrate into host circuitry and that pattern of host connectivity is primarily dependent on location of the transplant.

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Poster

668. Parkinson's Disease: Circuit Mechanisms

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Program#/Poster#: 668.19/V5

Topic: E.05. Brain-Machine Interface

Support: National Research Foundation of Korea

Title: Network correalates of the effects of repetitive transcranial magnetic stimulation on freezing of gait in patients with Parkinson's disease

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Abstract: Introduction: High-frequency repetitive transcranial magnetic stimulation (rTMS) over the lower leg primary motor cortical area can alleviate freezing of gait (FOG) in patients with Parkinson’s disease (PD). However, the response to high-frequency rTMS is highly variable between patients, and the mechanisms of action are also uncertain. The aim of this study was to identify the functional brain connectivity associated with improvement of FOG in response to high-frequency rTMS in patients with PD. **Methods:** Sixteen patients with PD (mean age 63.6 yrs) participated. All patients received high frequency rTMS (90% of resting motor threshold, 10 Hz, 1,000 pulses) over the lower leg primary motor cortical area of the dominant hemisphere (M1-LL) for 5 consecutive days. The FOG Questionnaire (FOG-Q) was performed before and immediately after rTMS. FOG-Q changes greater than or equal to 5 points were considered to the good responder group. Presence or absence of BDNF polymorphism was assessed and Resting-

state functional MRI (rs-fMRI) was acquired in all patients before rTMS and we performed seed to voxel analysis to assess connectivity of parietal opercular cortex and central opercular cortex in each patient. The laterality index was calculated to measure asymmetry in functional connectivity between both hemispheres. Various demographic and clinical characteristics and the laterality index of connectivity of rs-fMRI were compared between good and poor responder groups of rTMS. **Results:** Eight (50.0%) and 8 (50.0%) patients were classified as good and poor responders, respectively. There was no significant difference in age, sex, duration of PD, and Hoehn-Yahr stage between good and poor responder groups. In addition, severity of motor impairment and FOG-Q showed no significant difference between two groups. The number of Met heterozygote was significantly higher in the poor responder group than the good responder group ($p<0.05$). In the analysis of rs-fMRI, the laterality index of the central opercular cortex showed significantly higher asymmetry in the good responder group than the poor responder group ($p<0.05$). **Conclusion:** These results suggest that BDNF genotype the lateralization of connectivity of rs-fMRI can be used for designing individually-tailored rTMS to reduce FOG in patients with PD (Supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2017R1A2A1A05000730, NRF-2016R1A2B4012054)).

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Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 669.01/V6

Topic: C.03. Parkinson’s Disease

Support: AA023165

AA017347

AA017168

NS075097

AG047366

Michael-J-Fox foundation

Title: Functional network differences in aging with HIV infection and Parkinson's disease

Authors: *E. M. MULLER-OEHRING[1,2], J. Y. HONG[2], T. MARTIN[3], H. M. BRONTË-STEWART[3], K. L. POSTON[3], R. R. GOODCASE[2], J. A. KARPF[2], W. CHU[2], E. V. SULLIVAN[1], A. PFEFFERBAUM[2], T. SCHULTE[2,4]
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Abstract: Combination antiretroviral therapy (cART) has allowed individuals infected with Human Immunodeficiency Virus (HIV) to reach typical life expectancy. Now, HIV positive individuals are subject to age-related processes including neurodegenerative diseases similar to that of Parkinson's disease (PD), given that both diseases affect subcortico-cortical pathways. We compared neural networks in 20 older healthy controls (HC), 20 HIV-infected individuals, and 22 individuals with PD using resting-state functional connectivity MRI. Functional connectivity (fc) was determined using the Stanford 90ROI functional atlas (findlab.stanford.edu/functional_ROIs.html) for ROI-to-ROI analysis testing differences in interregional fc among the 3 groups (pFWE<0.05, 2-tailed). Significant group differences were observed for fc between parietal and frontal, thalamic, and cerebellar regions, and between left and right motor cortices. Follow-up analysis revealed a graded pattern from strong fc in PD to weaker fc in HIV and weakest fc in HC between left angular cortex and precuneus, posterior and middle cingulate, and superior frontal regions, and the opposite graded pattern from weak fc in PD, stronger fc in HIV, and strongest fc in HC between parietal-orbitofrontal regions. Older age in HIV was associated with greater angular-precuneus fc (r=.65, p=.002). Specifically, HIV showed weaker bilateral thalamo-precuneus fc than HC, in whom greater thalamo-precuenus fc correlated with faster fine finger movement (FFM; all p's <0.05). PD most notably exhibited weaker fc than HC and HIV between left and right motor cortices and between cerebellar vermis and parietal cortices, with the latter being associated with slower left hand FFM performance in PD (r=.55, p=.007). Together our findings indicate both, a graded pattern of fc alteration with HIV being in-between HC and PD, and diagnosis-specific neurofunctional consequences for intrinsic interregional brain networking that have meaning for motor skills. AA023165, AA017347, AA017168, NS075097, AG047366, Michael-J-Fox foundation

Disclosures: E.M. Muller-Oehring: None. **J.Y. Hong:** None. **T. Martin:** None. **H.M. Brontë-Stewart:** None. **K.L. Poston:** None. **R.R. Goodcase:** None. **J.A. Karpf:** None. **W. Chu:** None. **E.V. Sullivan:** None. **A. Pfefferbaum:** None. **T. Schulte:** None.

Poster

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Topic: C.03. Parkinson's Disease

Support: NIH R01 NS075012

NIH T32 NS082169

Title: Changes in free-water along motor tracts in parkinson's disease and atypical parkinsonian syndromes

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Abstract: Diffusion imaging (dMRI) could provide a unique method for non-invasive in vivo quantification of Parkinson's disease progression. The objective of this work was to explore the changes in free-water along key white matter tracts in the brain that are important in movement in Parkinson's disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP). These tracts include the corticostriatal, cerebello-thalamo-cortical, and corticospinal tracts. The study examined a cohort of 38 controls, 46 PD patients, 16 MSA patients, and 19 PSP patients who each received two MRI scans one year apart (baseline and 1-year). A unique probabilistic tractography algorithm was used to derive these motor tracts and average free-water along the tracts in each axial slice was quantified. These values were then compiled to create free-water profiles. An ANOVA, with covariates using age and sex, was conducted at each axial slice for each tract profile to determine group effects. Additionally, a cross-sectional analysis was conducted correlating area under the curve (AUC) of the free-water profiles with clinical scores at baseline and 1-year separately. The large majority of all motor tracts were found to have significantly [$p<0.05$, false discovery rate (FDR) corrected] increased free-water in PSP compared to controls. Additionally, portions of the cerebello-thalamo-cortical tract showed significantly [$p<0.05$, FDR corrected] increased free-water in MSA compared to controls. Free-water AUC was found to significantly correlate with the Purdue Pegboard test performance [baseline: $R^2=56.4\%$, $p<0.001$; 1-year: $R^2=59.9\%$, $p<0.001$] and Unified Parkinson's Disease Rating Scale (UPDRS) scores [baseline: $R^2=43.0\%$, $p=0.003$; 1-year: $R^2=43.0\%$, $p=0.003$] at baseline and 1-year time points. Evidence has been provided for structural alterations within important tracts relevant to movement. These results further show that the structural alterations correlate with clinically relevant measures such as the Purdue Pegboard and UPDRS.

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Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

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Program#/Poster#: 669.03/V8

Topic: C.03. Parkinson’s Disease

Support: Chinese NSF 81600982

Title: Functional connectivity in the somatosensory network in the akinetic-rigid and tremor Parkinson's disease patients

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Abstract: Parkinson’s disease (PD) is a neurodegenerative disorder characterized by movement disorder. Convergent evidence has indicated that PD patients also experience an array of somatosensory problems. The underlying mechanism of somatosensory deficits in PD is still poorly understood. In addition, the symptoms are also assumed to contribute to the deficits in sensorimotor integration which is considered to degrade motor performance in PD. The goal of this study was to characterize the functional connectivity (FC) in the cortical somatosensory network and the correlation between the activation pattern of somatosensory network and the motor symptoms in different PD types. To this end, we used the resting-state functional magnetic resonance imaging (fMRI) to explore the FC change in the cortical somatosensory network,

including BA1, 2, 3A, 3B, 5 and 7, which were extracted from the Julich Cytoarchitectonic Mapping. We analyzed the mean FC of somatosensory network in 35 patients, 21 akinetic-rigid Parkinson's disease (PD AR) and 14 tremor Parkinson's disease (PDT), along with 20 age-matched healthy controls (HC). All Parkinson's patients were evaluated by Unified Parkinson's Disease Rating Scale (UPDRS). Our data demonstrated that the widespread deficits in FC within the somatosensory network in the PDAR subjects, as compared to HC ($P<0.01$, Bonferroni correction) and PDT subjects ($P<0.001$, Bonferroni correction). There is no significant difference between HC and PDT in mean Fisher's r-to-Z score for all connections within the somatosensory network. In addition, the rigidity score of PDAR is significantly negative linear related to the mean FC of somatosensory network ($P<0.005$). Taken together,the results indicated that the somatosensory network may play an important role in PDAR subtype and the FC strength of somatosensory network may be related to the motor performance in PD.

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Poster

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Topic: C.03. Parkinson's Disease

Support: FONDECYT 11130534

Anillo ACT1416

Title: Substantia nigra T1 maps for the diagnosis of Parkinson´s disease

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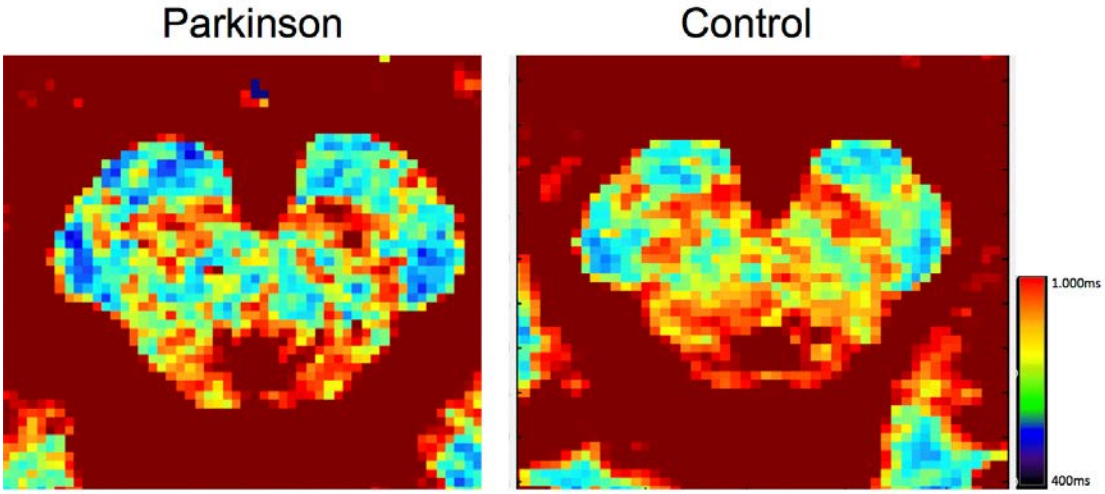
Abstract: The death of dopaminergic neurons in the substantia nigra (SN) pars compacta is the pathological hallmark of Parkinson disease (PD). Although numerous imaging techniques have been used to evaluate PD, most of them are based in qualitative MR images rather than quantitative MR images. Qualitative MR are very sensitive of acquisition parameters and the way of the analysis is performed. We propose to study this anatomical region using quantitative T1 maps that estimate the spin relaxation time for each pixels which could be related with the integrity of the tissue. We proposed that the T1 value (measured in ms) would be related with the degree of nigral degeneration in PD as compared with healthy controls (HC). Also we compared

the asymmetry in SN T1 values in PD subjects. Patients and Methods: PD patients diagnosed according to the London brain Bank criteria were included. Patients were scanned in a 1.5T Achieva Philips scan and a T1 mapping was performed using a sequence that employs two non-selective inversion pulses with inversion times ranging from 20ms to 2000ms, followed by 8 segmented readouts for 8 individual images. T1 values were computed on a pixel-by-pixel basis using an in-house software (Matlab, Natick, MA). Healthy volunteers were scanned as controls. Results: Ten PD patients and 10 HC were included. T1 maps showed a different pattern between PD and HC. The average T1 relaxation time of the whole SN between HC and PD was significant different (Figure). No differences were found in the SN in PD between more and less affected sides. Segmental analysis in the T1 values demonstrated significant differences in the middle and posterior section of the SN between HC and PD groups. Conclusions: T1 map is a quantitative technique that could provide new information for the diagnosis and follow-up of PD patients. Additionally its quantitative properties allow to compare the results between different patients and to evaluate progression in a quantitative and objective way. Larger and prospective studies are needed to confirm these findings.CJ is supported by FONDECYT 11130534 and MA by Anillo ACT1416.



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Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 669.05/V10

Topic: C.03. Parkinson’s Disease

Title: Changes in motor subtype designation of Parkinson's disease patients from two cohorts

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Abstract: Background: Distinct motor subtypes of PD have been identified through both clinical observation and data-driven approaches. However, the extent to which motor subtypes are mutable during disease progression is not fully known.
Methods: We used the Parkinson's Progression Markers Initiative (PPMI) database of 423 newly diagnosed PD patients and the National Institute of Neurology and Neurosurgery database from Mexico (UNAM) of 197 PD patients. Using hierarchical correlational clustering, in both cohorts we found distinct Tremor Dominant (TD), Axial Dominant (AxD), Appendicular Dominant (ApD), Rigidity Dominant (RD), and Postural Instability and Gait Disorder/Dominant (PIGD) groups. For each motor assessment time point, we mathematically assigned patients to one of these five subtypes. We then converted these categories to an ordinal scale by assigning each subtype a numerical value from 1 to 5. For patients with inconsistent subtypes over time, we computed relative subtype frequencies over time using a bin width of 3 months to produce population-level averages. We analyzed subtype drift over time using univariate analysis, ANOVA, and regression.
Results: Subtypes for 52% and 72% of patients within the PPMI and UNAM cohorts respectively fit criteria for at least two different subtypes across time points. For the PPMI cohort, 59.3% of patients were categorized as TD and 21.4% as PIGD. By 4.5 years after diagnosis, these values shifted to 40.6% and 35.9% respectively. Similarly, for the UNAM cohort, 60% of patients were categorized as TD and 21% as PIGD soon after diagnosis. By 6 years, these numbers shifted to 37% and 42% respectively. By ANOVA, there was a significant increase in subtype values over time within the PPMI cohort, $p < 0.001$, and within the UNAM cohort, $p < 0.001$. In other words, on the spectrum from TD to PIGD, the cohort as a whole progressed away from a TD phenotype with disease progression. A linear regression model of motor subtype dependent on time suggests that subtype increased by about 0.22 units per year after diagnosis within the PPMI group ($p < 0.001$) and by 0.14 units per year after diagnosis within the UNAM cohort ($p < 0.001$). These results demonstrate that PD motor subtypes may change or progress over time.
Conclusions: PD subtypes are stable for some patients and unstable for others. By frequency, more patients are classified as TD soon after diagnosis. There is an overall shift away from TD and towards PIGD with disease progression.

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Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

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Topic: C.03. Parkinson’s Disease

Title: Altered cortico-striatal functional connectivity in REM sleep behavior disorder with subtle motor dysfunction

Authors: G. YAMADA[1], *Y. UEKI[2], N. OISHI[4], T. OGURI[1,5], A. FUKUI[3], M. NAKAYAMA[3], N. MATSUKAWA[1]
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Abstract: Subtle motor dysfunction is reported to be a high-risk factor of neurodegenerative disorders in REM sleep behavior disorder (RBD), however, there are few studies as to evaluate the motor function. We investigate whether finger tapping movement is already impaired in some patients with RBD and if so, it is attributed to the nigrostriatal degeneration and/or sensorimotor network abnormality. Twenty patients with RBD and twenty age-matched healthy controls (HC) were included. Sixteen patients were diagnosed as RBD by polysomnography and four patients were determined as probable RBD by the Mayo Sleep Questionnaire. In finger tapping, participants were instructed to tap their index finger and thumb as rapidly and as widely as possible during 15 seconds. Mean amplitude, peak open velocity and peak close velocity were recorded using a magnetic sensing device. When either of these parameters in RBD is less than two standard deviations of that in HC, these RBD patients were classified as “poor performer”. DAT SPECT and Resting-state fMRI were performed and compared between HC and poor performer of RBD. Six RBD patients were classified as poor performer. The laterality index |Right-Left|/((Right+Left)/2)) of SBR in posterior putamen was significantly higher in poor performer of RBD compared with HC. Moreover, they exhibited decreased functional connectivity between striatum and cortical areas compared to HC. These results revealed the nigrostriatal degeneration and altered cortico-striatal network in RBD patients with poor finger tapping performance. Stratification of RBD patients with finger tapping might be useful for early diagnosis of pre-clinical neurodegenerative disorders.

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Poster

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Topic: C.03. Parkinson’s Disease

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P30 NS076408

Udall P50 NS098573

Title: Individualized tractography-based parcellation of the globus pallidus pars interna using 7-Tesla magnetic resonance imaging in movement disorder patients prior to deep brain stimulation surgery

Authors: *R. PATRIAT[1], Y. DUCHIN[2], J. NIEDERER[2], C. LENGLET[2], J. AMAN[3], S. COOPER[3], J. VITEK[3], N. HAREL[2]
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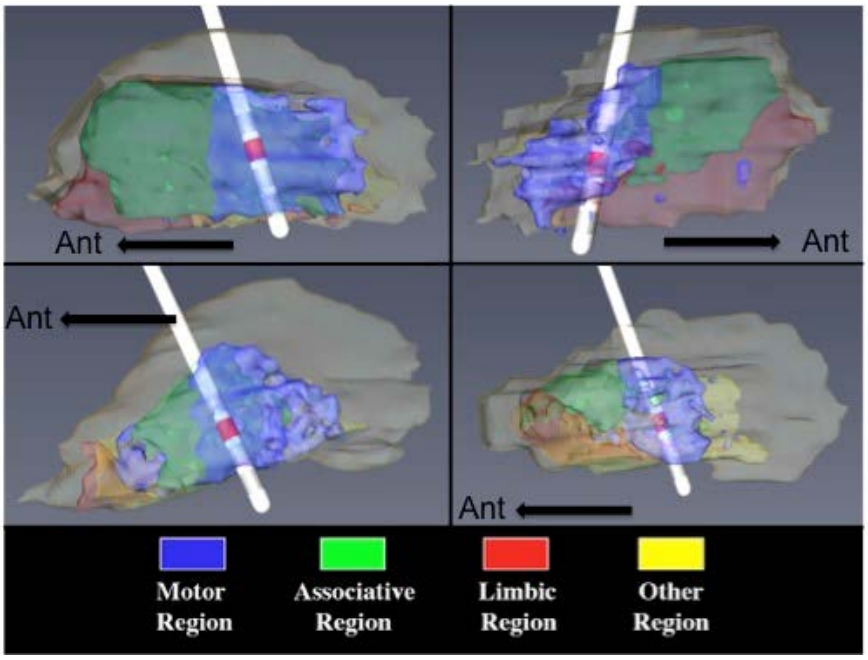
Abstract: The success of deep brain stimulation (DBS) surgeries for Parkinson’s disease relies on the accurate placement of an electrode within the motor portion of subcortical brain targets with the goal of maximizing the patient’s benefits while minimizing side effects. Today’s targeting methods do not ensure such accuracy and it is estimated that 15-34% of DBS procedures require revisions. Common targeting methods typically consist in fitting template information onto the patient’s anatomy, which results in errors in the determination of the location, shape, size and orientation of the actual DBS targets. These inaccuracies may engender the DBS electrode to be placed either outside of the target or within the target but not in the motor territory, thus, causing debilitating side effects. We have previously demonstrated that 7-Tesla magnetic resonance imaging (MRI) can be used to produce high-resolution images enabling accurate visibility of the basal ganglia structures. In this study, we show that 7-Telsa diffusion MRI can be used to uncover the functional territories of the globus pallidus pars interna (GPi) in Parkinsonian patients prior to their DBS surgery. We show a consistent organizational pattern of functional territories across patients with the motor region in the posterior region of the GPi immediately followed anteriorly by the associative and limbic territories (Figure 1). We validate our results using micro-electrode recording obtained during the surgery. Additionally, we use post-surgery images to identify the final location of the DBS electrode and stimulation contacts for each patient and include information about the DBS programming to further validate

our results (Figure 1). This method has the potential to greatly improve targeting for DBS surgeries, not only for Parkinson's disease but also other movement disorders.



Disclosures: **R. Patriat:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences. F. Consulting Fees (e.g., advisory boards); Cardionomic. **Y. Duchin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences. **J. Niederer:** None. **C. Lenglet:** None. **J. Aman:** None. **S. Cooper:** None. **J. Vitek:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences. F. Consulting Fees (e.g., advisory boards); InsighTec, Medtronic, Abbott, Boston Scientific. **N. Harel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences.

Poster

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Topic: C.03. Parkinson's Disease

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NINDS NS075321

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NINDS NS097437

Title: Abnormal BOLD fMRI resting state lag structure in idiopathic Parkinson disease

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Abstract: Degeneration of nigrostriatal dopaminergic neurons with consequent dysfunction of neural circuits involving basal ganglia, thalamus, and cerebral cortex contribute to the motor and cognitive manifestations of Parkinson disease (PD). Striatal function affects motor and cognitive domains with putamen more directly affecting movement and caudate influencing cognition. In conventional resting-state fMRI, functional connectivity (FC) is defined in terms of blood oxygen level dependent (BOLD) signal temporal correlations at zero-lag. Altered cortical-striatal FC has been reported in PD, albeit with substantial variability across laboratories. A recently described, alternative approach (LAGS), based on evaluating BOLD signal temporal delays, has revealed highly reproducible propagation patterns of infraslow (less than 0.1 Hz) activity in normal individuals. We applied this LAGS strategy to determine whether putamen and caudate exhibit different temporal relationships with respect to cortical regions. We studied 62 adults with idiopathic PD (age 64±6.8 yrs) off meds overnight and 22 demographically matched, healthy controls (age 65± 9.6 yrs). Statistical significance was assessed clusterwise in seed-based lag maps using threshold-extent criteria computed by extensive permutation resampling. LAGS analysis revealed that, in controls, anterior cingulate, anterior insula and visual cortex are early but motor cortex is late with respect to caudate. In PD, anterior cingulate and visual cortex lead caudate by a smaller temporal lag whereas motor cortex now leads the caudate and anterior insula follows rather than leads caudate. In controls, dorsal anterior cingulate (dAcc) leads visual, pre-motor, putamen and motor cortex. In PD, dAcc leads visual, pre-motor and motor cortices but less so than in controls. Putamen, however, now leads dAcc instead of following. Thus, signal propagation between selected cortical regions and striatum is markedly altered in PD and, in several instances, reversed in direction. Moreover, these effects are distinct in putamen vs. caudate. Conventional (i.e., zero-lag) FC analysis of the same data showed only comparatively modest effects (moderately reduced FC in PD). These results demonstrate that dysfunction in PD manifests in the lag structure of intrinsic brain activity much more than in correlation-based FC analyses, and may provide insight into potential different functional consequences of dopaminergic drugs on caudate and putamen.

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Poster

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Support: AA023165

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NS075097

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Michael-J-Fox foundation

Title: Frequency dependent brain signal oscillations in HIV infection and Parkinson's disease modulated by age

Authors: J. Y. HONG[1], E. M. MÜLLER-OEHRING[2], H. M. BRONTË-STEWART[3], T. MARTIN[3], K. L. POSTON[3], E. V. SULLIVAN[2], *A. PFEFFERBAUM[1], T. SCHULTE[1,4]
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Abstract: Over 30 years after the epidemic of HIV infection, and with the advances of antiretroviral therapy, patients with human immunodeficiency virus (HIV) infection are now aging and may be at risk for age-related neurofunctional decline similar to that of Parkinson's disease (PD), given that both diseases affect subcortico-cortical pathways. We examined resting-state functional MRI multiband frequency power in 20 older healthy controls (HC), 20 HIV-infected individuals, and 22 individuals with PD. To test the effect of aging on intrinsic neurofunctional properties of HIV and PD relative to HC, we measured fMRI activity across different frequency bandwidths by quantifying the amplitude of low frequency fluctuation (ALFF) for the frequency power spectrum for each voxel across three bandwidths: Low (LF: 0.01-0.027Hz), middle (MF: 0.027-0.073Hz) and high frequency (HF: 0.073-0.17Hz). Frequency oscillation power has been linked to neuronal physiological properties. Overall, subcortical regions exhibited higher ALFF values in the HF band, whereas cortical regions had higher ALFF

values in the MF and LF bands. Regardless of diagnosis, older age was associated with greater HF oscillation power in the pallidum and greater LF power in temporal cortices. In HC, older age was associated with greater HF and LF power in the basal ganglia, hippocampal and brainstem areas. Older age in HC was negatively correlated with HF power in the precuneus, medial and dorsolateral prefrontal cortices. HIV showed greater HF power in the basal ganglia with older age. In PD, however, older age was mainly related to less HF power in the cuneus. In sum, both HC and HIV showed positive age-HF power relations in the basal ganglia, which were not seen in PD. Lower precuneus and medial prefrontal HF power with healthy aging was associated with lower scores in memory span. In HIV and PD, greater LF power in the basal ganglia correlated with lower scores in the dementia rating scale. Our findings suggest that normal aging changes subcortical and cortical neural properties that can partially account for working memory limits experienced in older age. Aging with HIV was associated with enhanced alteration of basal ganglia neural properties that had ramifications for global cognitive functioning similar to PD (where basal ganglia properties were independent of age). This study is novel in identifying age-related characteristics in BOLD oscillation power in aging HIV and PD patients. Age-related oscillation power changes may serve as a landmark for understanding the brain functioning in healthy aging and with neurodegeneration. AA023165, AA017347, AA017168, NS075097, AG047366, Michael-J-Fox foundation

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Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 669.10/V15

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[1], M. MUTHALIB[2], R. PEGORARO[2], L. ROEDER[2], I. STEWART[2], S. SMITH[2], N. WHITE[2]
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Abstract: Objective: To determine how prefrontal cortex activation is affected during concurrent cognitive and balance tasks in people with Parkinson’s disease (PD).
Background: In PD, reduced executive function has been associated with poorer quality of life,

decreased activities of daily living and increased balance and gait disturbance. Neural circuits involving activation of prefrontal cortex and involved in executive function are thought to be critical for control of balance and gait.
Methods: Functional near-infrared spectroscopy (fNIRS) imaging was used to determine how prefrontal cortex activation was affected during concurrent cognitive and balance tasks. Pre-frontal cortex alterations in concentration of oxy- (O2Hb) and deoxy-haemoglobin (HHb) in cerebral microcirculation blood vessels were recorded using fNIRS during performance of an executive function task (verbal fluency). During this task, participants were either seated or standing quietly on a force plate. Early stage PD, healthy age matched control, and young participants were assessed according to the following protocol repeated 5 times during sitting and standing: Baseline (30s), Verbal Fluency (30s), Week Days Recital (30s).
Results: Both the young, control and the PD groups had similar performance in the verbal fluency and the week day recital tasks. In the young group, neuronal activation during the verbal fluency task (relative to baseline) caused a change in regional blood flow, which was characterized 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. Similar, but reduced changes were observed for the age-matched control group. 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 all groups.
Conclusions: These changes in O2Hb indicate that activation of the DLPFC is reduced in PD during executive function tasks. During standing activation of the DLPFC is further reduced, in contrast to young and control participants who have increased bilateral activation.

Disclosures: G. Kerr: None. **M. Muthalib:** None. **R. Pegoraro:** None. **L. Roeder:** None. **I. Stewart:** None. **S. Smith:** None. **N. White:** None.

Poster

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Location: Halls A-C

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Topic: C.03. Parkinson’s Disease

Support: NIH Intramural Research Program

Title: Connectivity correlates of cognitive deficits in deep brain stimulation therapy for Parkinson disease

Authors: *S. C. NANIVADEKAR[1], Q. YANG[1], P. TAYLOR[2], C. LUNGU[1], S. HOROVITZ[1]
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Abstract: Subthalamic Nucleus Deep brain stimulation (STN-DBS) treats motor symptoms in Parkinson disease (PD) patients by stimulating the STN. PD patients show cognitive decline in executive functions after STN-DBS surgery [Demeter, 2017]. Using diffusion-weighted-imaging (DWI) and clinical data, we investigated the potential neural correlates of cognitive side effects. We hypothesize that the perturbation of task-specific functional networks might lead to cognitive deficits. We recorded the Stroop Color Word Task and Verbal Fluency Task scores from 23 patients with DBS pre-operatively and at 3 months post-operatively as measures of executive function and language. The Stroop scores significantly decreased from pre-Op (50.68±9.32) to post-Op (42.45±7.52) and the Fluency scores decreased significantly from pre-Op (51.57±10.54) to post-Op (44.76±10.37). T1, T2, and DWI were collected pre-Op and T2 images and CT scans were collected post-Op. We modeled patient-specific DBS contacts using DBSproc [Lauro, 2015]. Volumes of tissue activated (VTA) were calculated based on stimulating voltage and impedance at 3 months after DBS. Diffusion data was preprocessed in TORTOISE [Pierpaoli, 2010]. We performed probabilistic tractography between the VTA to the functional networks for the Stroop and Fluency task defined by fMRI studies [Leung,2000; Schlosser,1998], and tested them in a 1-sample t-test with changes in behavioral scores as covariates. For significantly correlated clusters (p-value <0.05), we computed the correlation between the average number of voxels within each ROI and the change in scores. For this analysis, an $R^2 > 0.6$ and an even distribution was considered to be a strong correlation. Voxelwise correlation showed that an increase in connectivity to the Caudate, Putamen and Globus Pallidus led to worsening of Stroop scores with R^2 of 0.70, 0.62, 0.646 respectively. Increased connectivity to the Stroop network showed greater performance deficits (R^2= 0.694). Overall effect in the Fluency network was not strong (R^2=0.22), however the Insula connectivity showed a strong negative correlation (R^2= 0.699) with the deficits in Fluency scores. Stimulating the insula in the Fluency Task network improved performance, suggesting a beneficial compensation by the DBS stimulation. However, stimulating areas of the Stroop network resulted in a decline in performance suggesting that avoiding these clusters could prevent cognitive decline of executive functions. Our findings suggest changes in connectivity to functionally relevant regions in the brain as neural correlates of cognitive deficits.

Disclosures: S.C. Nanivadekar: None. **Q. Yang:** None. **P. Taylor:** None. **C. Lungu:** None. **S. Horovitz:** None.

Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

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Program#/Poster#: 669.12/V17

Topic: C.03. Parkinson's Disease

Support: NIH Intramural Research Program

China Scholarship Council PhD Exchange Program

Title: White matter integrity changes in stroop color words interference tasks in Parkinson's Disease

Authors: *Q. YANG[1,3], S. NANIVADEKAR[1], P. TAYLOR[2], C. LUNGU[1], S. HOROVITZ[1]
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Abstract: Parkinson's Disease (PD) is a common movement disorder thought to be caused, in part, by dopaminergic neurons degeneration in substantia nigra pars compacta. PD is recognized by its motor symptoms, however, nonmotor symptoms, including cognitive deficits, are reported in PD patients and significantly reduce quality of life. Stroop Color Words interference task (SCW) is commonly used to test executive function deficits in PD patients. How white matter ingegrity affects SCW is not fully known. In our studies, SCW task scores were collected, by a neuropsychologist, from 20 non-demented on-medication PD subjects (age range 44-75,11 females). Diffusion Tensor Images (DTI) were collected at 3T scanner. Images preprocessing was completed in TORTOISE. The tractographic Connectivity Analysis Toolbox(FATCAT) was used for tractography analysis among regions of the Stroop Network, defined from functional MRI studies (Leung HC, et al, 2000). We performed a 1-sample t-test of the FA for the tracts connecting the Stroop Network ROIs ($p<0.005$, cluster size >100) using the SCW scores as covariates. The results showed that connectivity to clusters in left superior temporal gyrus(r=.72), right transverse temporal gyrus(r=.76), had a strong positive correlation with the SCW scores. The tracts affected include left superior longitudinal fasciculus, inferior fronto-occipital fasciculus. The left superior frontal gyrus(r=-0.89) and right middle frontal gyrus(r=-.90) show negative correlations with SCW scores. The tracts affected include the anterior thalamic radiation and right superior longitudinal fasciculus. As previous reported, (Catherine G, et al, 2013, Rebecaa J. T, et al, 2013) we showed that FA values of white matter were positively correlated with Stroop performance. We also showed, in our PD patients, that increased connectivity to some regions could reflect cognitive deficits.
References:
Gallagher, et al. J Int Neuropsychol Soc. 2013;5;19(3) 349–354. Leung,et al. Cereb Cortex(2000) 10 (6): 552-560. Theilmann,et al. Front Neurol. 2013; 4: 37.

Disclosures: Q. Yang: None. **S. Nanivadekar:** None. **P. Taylor:** None. **C. Lungu:** None. **S. Horovitz:** None.

Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

Location: Halls A-C

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Program#/Poster#: 669.13/V18

Topic: C.03. Parkinson’s Disease

Support: GE Global Research

Title: Use of functional MRI to assess effects of deep brain stimulation frequency on brain activation in Parkinson Disease

Authors: *M. DIMARZIO[1], I. HANCU[4], E. FIVELAND[4], J. PRUSIK[2], S. JOEL[4], R. MADHAVAN[4], J. DURPHY[5], E. HANSPAL[5], D. SHIN[3], J. G. PILITSIS[2]
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Abstract: Introduction: Deep brain stimulation (DBS) is a well-validated treatment of motor symptoms in Parkinson’s disease (PD). While DBS has been used for many years, its mechanism of action remains unclear. With a recent change in labeling that allows MRI to be performed with DBS in the ON state, we present the first experience with functional MRI (fMRI) with subjects with DBS for PD. Specifically; we examine how frequency changes affect blood oxygen level dependent (BOLD) activation on fMRI. **Methods:** PD subjects with optimized DBS programming underwent fMRI with BOLD activation. Frequency was altered and fMRI obtained at various settings. To ensure that fMRI cycling and subject programmer cycling were synced, an electronics box coupled to electrocardiogram leads were integrated into workflow. Model-based voxel-wise General Linear Model (GLM) using the DBS-off data was used to determine which regions were more activated during the DBS-on periods with respect to the DBS-off periods. **Results:** Six of seven enrolled subjects had data able to be analyzed while the seventh had significant artifact preventing its use. Subjects differed in site implanted, subthalamic nucleus (STN)) for 5 and Globus pallidus interna (Gpi) for 1. In four patients, we showed motor deactivation at one frequency. Subject symptoms were primarily tremor in 2 subjects and hypokinetic in 4 subjects. The two subjects with hypokinetic symptomatology with bilateral STN DBS demonstrated dorsomedial prefrontal cortex activation at their optimal settings. **Discussion:** Our findings show that we are able to use fMRI to visualize BOLD activation that was caused by alterations in frequency. These findings will allow us to visualize the activation patterns that should be present when a subject’s frequency is in an optimal setting. Understanding these patterns, will allow us to improve the standard of care post DBS implantation by decreasing the amount of time it takes to choose the correct settings that would provide beneficial effects and eliminate side effects.

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Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 669.14/V19

Topic: C.03. Parkinson's Disease

Title: Frontostriatal functional connectivity is associated with both cognitive and motor symptoms in parkinson's disease

Authors: ***S. KANN**[1], P. MANZA[2], H.-C. LEUNG[3]
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Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder associated with depletion of dopamine neurons in the midbrain. While dopamine loss plays a role in both motor and cognitive deficits in PD, disease progression is heterogeneous, leading to strong individual differences in these symptoms. Specifically, motor symptoms may present as either akinetic/rigid or tremor dominant subtypes, and critically, cognitive symptoms are more often associated with the akinetic/rigid subtype. Impaired performance on executive function tasks are associated with altered basal ganglia-cortical functioning in PD patients. However, whether similarly altered connectivity plays a role in akinetic/rigid symptoms, independent of executive function scores, remains unknown. The present study therefore examined basal ganglia-cortical connectivity in relation to executive function and akinetic/rigid scores within PD patients. Using the Parkinson's Progressive Marker Initiative (PPMI) database, 93 participants with early stage PD (Hoehn and Yahr $\leq$ 2) were assessed for functional connectivity between the basal ganglia and the frontal regions in relation to executive function scores (M=-.36, SD=.79) as well as akinetic/rigid scores (M=10.18, SD=5.59). All regression analyses conducted controlled for patients' medication status (drug naïve=35) gender (f=35), study site, rest tremor (M=1.51, SD=1.55) and age (M=61.31, SD=10.31). Motor and cognitive measures were also related to measures of dopamine transporter (DAT) in the caudate and putamen. Replicating previous research, we found that rigidity scores negatively correlated to executive control scores, while DAT values from the caudate differentiated these two behavioral measures in that greater DAT were associated with better cognitive scores, while lower DAT were associated with greater rigidity symptoms.

Importantly, this differentiation was also evident in basal ganglia-cortical connectivity. Greater connectivity between the caudate and ventromedial prefrontal cortex was associated with lower scores on executive function, controlling for rigidity, while greater connectivity between the putamen/pallidum and ventromedial prefrontal cortex was associated with higher rigidity scores, controlling for executive function. These findings suggest that both rigidity and executive functioning symptoms are independently related to altered basal ganglia-cortical connectivity as well as depletion of striatal dopamine within PD. These shared neural correlates may offer insight into the disease progression associated with impaired cognition and akinetic/rigid symptoms within PD.

Disclosures: S. Kann: None. **P. Manza:** None. **H. Leung:** None.

Poster

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Location: Halls A-C

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Program#/Poster#: 669.15/V20

Topic: C.03. Parkinson’s Disease

Title: Alternations in striato-pallidal intrinsic functional connectivity as a prodrome of Parkinson’s disease

Authors: *E. DAYAN, N. BROWNER
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Abstract: Although the diagnosis of Parkinson’s disease (PD) remains anchored around the cardinal motor symptoms of bradykinesia, rest tremor, rigidity and postural instability, it is becoming increasingly clear that the clinical phase of the disease is preceded by a long period of neurodegeneration, which is not readily evident in terms of motor dysfunction. The neurobiological mechanisms that underpin this prodromal phase of PD remain poorly understood. Based on converging evidence of basal ganglia (BG) dysfunction in early PD, we set out to establish whether the prodromal phase of the disease is characterized by alternations in functional communication within the input and output structures of the BG. We analyzed resting-state functional MRI data collected from patients with REM sleep behavior disorder (RBD) and/or hyposmia, two of the strongest markers of prodromal PD, in comparison to age-matched controls. Relative to controls, subjects in the prodromal group showed reduced interhemispheric functional connectivity in each of the tested BG nuclei (putamen, caudate, pallidum) as well as reduced striato-pallidal inter- and intrahemshpric connectivity. The data suggest that local interactions between input and output BG structures may be disrupted already in the prodromal phase of PD.

Disclosures: E. Dayan: None. **N. Browner:** None.

Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

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Topic: C.03. Parkinson’s Disease

Support: NIH/NINDS: F32NS092290

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NIH/NINDS: NS097437

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St. Louis Chapter of the APDA

WashU ICTS/Barnes Jewish Hospital Foundation

Title: Functional connectivity deficits in Parkinson Disease

Authors: *C. GRATTON[1], J. KOLLER[2], B. SHANNON[4], D. J. GREENE[3], S. E. PETERSEN[1], J. S. PERLMUTTER[1], M. C. CAMPBELL[1]
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Abstract: Introduction: Parkinson Disease (PD) neuropathology includes proteinopathy and multiple neurotransmitter deficits impacting widespread brain regions, which clinically manifests as a heterogeneous pattern of motor, cognitive, and psychiatric features. Thus, a whole-brain network-level (*connectome*) description provides a window into the distributed deficits present in PD. This approach allows us to determine (1) the relative magnitude and specificity of functional deficits across brain systems, (2) whether differences extend to cross-system interactions, and (3) how systems-level differences are related to behavior.
Methods: We measured resting-state functional connectivity (FC) in a large, well-characterized dataset of participants with PD (N=107) and healthy older controls (HC, N=46). Connectomes were defined across a comprehensive sampling of cortical and subcortical systems, including striatal, thalamic, and cerebellar regions. We applied rigorous motion correction and quality assurance measures to reduce artifacts. Novel graph-based statistical methods were used to quantify differences between the PD and HC connectome and validated with split-half analyses.
Results: Connectomes differed significantly in PD relative to HC, and were characterized by selective system-to-system reductions in the magnitude of positive or negative FC. Cortical somatomotor (SM) systems exhibited the most robust differences in FC, both within the SM system itself and between SM and specific sensory, association, and subcortical systems.

Cerebellar and thalamic systems also differed strongly between PD and HC, primarily showing decreased magnitude of FC within each system and between these systems and cortical SM and sensory systems. Striatal FC displayed a similar pattern of differences as the thalamus, but was less strongly affected. A subset of system-to-system FC differences was related to motor and cognitive performance.
Conclusion: These findings indicate that PD is associated with modulations within and between selective cortical and subcortical systems. PD primarily diminished the magnitude of FC, suggesting a weakening of systems-level organization in SM, thalamic, and cerebellar systems. Notably, striatal FC deficits were less prominent than FC of downstream brain regions, which highlights the widespread, potentially emergent, functional effects of distributed neuropathology in PD. Furthermore, select FC deficits were related to specific behavioral deficits, potentially helping to explain the variability of clinical features exhibited in PD.

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Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

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Topic: C.03. Parkinson’s Disease

Support: CIHR MOP-136778

Title: Abnormal dynamic functional networks in Parkinson’s disease: A resting-state fMRI study

Authors: *J. KIM[1,2], M. CRIAUD[1,2], S. S. CHO[1,2], M. D. CIRARDA[1,2], A. MIHAESCU[1,2], S. COAKELEY[1,2], C. GHADERY[1,2], M. VALLI[1,2], M. F. JACOBS[1,2], S. HOULE[1], A. P. STRAFELLA[1,2,3]
[1]Res. Imaging Ctr., Campbell Family Mental Hlth. Res. Institute, CAMH, Toronto, ON, Canada; [2]Div. of Brain, Imaging and Behaviour – Systems Neurosci., Krembil Res. Institute, UHN, Toronto, ON, Canada; [3]Morton and Gloria Shulman Movement Disorder Unit & E.J., Safra Parkinson Dis. Program, UHN, Toronto, ON, Canada

Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by nigrostriatal dopamine depletion leading to whole-brain neural circuit changes (Khoo et al., 2013, Neurology, 80, 276-281; Weingarten et al., 2015, Neurosci Biobehav Rev, 59, 16-52). There have been previous studies showing altered functional connectivity in PD patients using static resting-state functional MRI(rs-fMRI) (Göttlich et al., 2013, PLoS One, 8, e77336; Sharman et al., 2013, Mov Disord, 28, 447-454). However, dynamic resting-state functional connectivity network (d-FNC) in PD remains largely unknown. In this study, we aimed to examine time-varying aspects of

functional network connectivity and topological properties in PD. Thirty-one PD patients ON medication (65.7±7.2 years) and twenty-four healthy controls (64.5±8.3 years) were included in the analyses. Resting-state fMRI data were collected in a GE 3T scanner (TR = 2s, 8 min 24 sec duration, eyes closed). Pre-processing was performed using SPM 12: motion correction, normalization to the MNI template, and spatial smoothing with a 6 mm Gaussian kernel. Using group spatial independent component analysis in GIFT toolbox, the preprocessed rs-fMRI data were decomposed into functionally relevant brain networks, resulting in 44 independent components (ICs). In dynamic functional connectivity (FC) analysis based on previous studies (Allen et al., 2014, Cereb Cortex, 24, 663-676), time-varying covariance matrices were computed using a sliding windows approach (TRs = 44, 1 TR steps) and were clustered two discrete FC states using K-mean clustering methods. We, then, compared the temporal properties: dwell time of state and number of state transitions. Dynamic FC analysis revealed that compared to HC, PD patients spend significantly shorter time in state I (a state which occurs frequently and has weak FC between components) and longer time in state II (a rarer state but with stronger FC pattern). The UPDRS motor symptom score was positively correlated with the number of the state transitions and negatively correlated with the dwell time of state I in PD patients. Our findings provide new insight into understanding the role of the dynamic FC network in PD which is not as well characterized. This research will provide a better understanding of the pathological mechanisms of PD.

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Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

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American Parkinson Disease Association (APDA)

NINDS NS097437

Title: Functional connectivity abnormalities in Parkinson and Alzheimer disease are more similar than different

Authors: *J. S. PERLMUTTER[1], A. TANENBAUM[3], M. CAMPBELL[4], A. MITRA[6], J. KOLLER[5], A. Z. SNYDER[2], B. M. ANCES[7]
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Abstract: Resting state fMRI (RS-fMRI) permits investigation of the physiological integrity of specific functional systems. This approach has been increasingly applied since the initial demonstration of reduced functional connectivity (FC) within the default mode network (DMN) in Alzheimer disease (AD), a compelling finding as the DMN is integral to episodic memory, which characteristically is impaired early in the course of AD. Similarly, RS-fMRI frequently demonstrates altered striatal FC in Parkinson disease (PD). However, the specificity of these FC effects with respect to degenerative condition has not been systematically investigated. We evaluated FC in 78 people with PD vs. 31 age-matched controls ($Control_{PD}$) and 88 symptomatic AD participants vs. 57 age-matched controls ($Control_{AD}$). FC was assessed using seed-based correlation in 6526 regions of interest defined by dividing all gray matter into 6 mm cubes. Denoising was accomplished by a CompCor-like procedure with the signal averaged over the whole brain included as a nuisance regressor. Scan protocol differences between the PD and AD studies precluded direct comparison of the functional data acquired in each affected cohort. Accordingly, the specific effects of degenerative condition (PD vs. AD) were evaluated by comparison of affected - control FC differences in both conditions. Affected - control FC differences in both conditions were remarkably similar. The most prominent effect in both PD and AD was comparably reduced FC of the somatomotor (SMN) network. Loss of FC was also observed in subcortical structures. Loss of FC in the default mode network (DMN) was not prominent in either AD or PD. Topographic similarity of FC change was computed by evaluating the $(PD - Control_{PD}) \cdot (AD - Control_{AD})$ vector dot product along each column of the difference matrices. Inspection of these results revealed a striking topographic similarity of FC changes highlighting the SMN, visual and infero-temporal cortex, and anterior thalamus, but not the DMN. In neither PD nor AD did FC differences localize to the most pathophysiologically abnormal parts of the brain (i.e., putamen and brainstem in PD, medial temporal lobe and DMN in AD). Rather, the common topography of affected - control differences resembles the effects of sleep in healthy, young individuals. Although sleep disturbances are well documented in both PD and AD, the sign of the presently observed effects (loss of FC in primary cortices) is opposite to that which would be expected on the basis of excessive daytime sleepiness in affected individuals. The pathophysiological significance of these observations presently is uncertain.

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Poster

669. Parkinson's Disease: Human Brain Imaging and Recording

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Topic: C.03. Parkinson’s Disease

Support: KAKENHI 15K10374

Title: Beta oscillatory activity of single neurons in the subthalamic nucleus in patients with Parkinson’s disease

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Abstract: Introduction: The subthalamic nucleus (STN) is a common target for deep brain stimulation (DBS) for treatment of Parkinson’s disease (PD). Recording of local field potentials in the STN in PD patients has shown increased beta-band activity, which is related to akinesia. On the other hand, analysis of neural activity of a single neuron in PD patients has shown increased neuronal firing in the STN; increased neuronal firing in the STN activity is associated with increased inhibitory drive to the motor thalamus via output nuclei of the basal ganglia, which could cause akinesia. These findings suggest that both beta-band activity and increased neuron firing in the STN are involved in akinesia. However, the relationship between beta-band activity and firing rate in the STN is unclear. Because the dorsal part of the STN is a motor area, we hypothesized that there would be a relationship between the STN motor area and the distribution of beta-band activity, which is related to motor symptoms (akinesia). In this study, we investigated the beta-band activities of single neurons and analyzed their relationships with the neuronal firing rate. In addition, we investigated the relationship between the STN motor area and the distribution of beta-band activity. **Methods:** We analyzed the frequencies of 119 single neurons in 10 patients with advanced PD who underwent implantation of deep brain stimulation electrodes in the STN. The neurons were classified as beta-band neurons (neurons with significant oscillatory activity at the beta-band) and nonoscillatory neurons (neurons without significant oscillatory activity at any band). Firing rates, distributions within the STN, and the proportions of neurons responding to passive joint movement (kinesthetic neurons) were compared between the 2 groups. **Results:** Of the 119 neurons, 16 (14%) and 83 (70.0%) were beta-band neurons and nonoscillatory neurons, respectively. The firing rate of beta-band neurons was significantly higher than that of nonoscillatory neurons (median firing rates, 48 Hz vs. 25 Hz, $p < 0.05$). Beta-band neurons were widely distributed within the STN, and there was no significant intergroup difference in neuron distribution between the dorsal STN and the ventral

STN. We did not note any significant intergroup difference in the proportion of kinesthetic neurons. **Conclusion:** The higher firing rate of beta-band neurons was consistent with the firing rate model of akinesia. The dorsal STN is a motor area, but the beta-band activity of a single neuron may not specifically reflect the motor symptoms of PD because of the wide distribution of beta-band neurons.

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Poster

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Title: Neural correlates underlying reward processing and decision-making in Impulse Control Disorder in Parkinson´s Disease

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Abstract: Background: Impulse Control Disorders (ICD) is a frequent and severe psychiatric complication in Parkinson's disease (PD) whose physiopathology is poorly understood. **Objectives:** To investigate the functional neural basis of decision-making in PD-ICD subjects

using a modified version of the Iowa Gambling Task (IGT) paradigm.
Material and methods: 18 PD-ICD patients, 17 PD non-ICD patients and 18 healthy controls (HC) matched for age, gender and education, underwent functional MRI (fMRI) scanning while performing a modified version of the IGT using a block experimental design. The task was divided in 3 sections: response to positive, negative and mixed feedback. Whole-brain, Region-of-Interest (ROI) and multivariate functional connectivity analyses were performed.
Results: The PD-ICD group showed increased activation across the 3 conditions compared to HC in prefrontal cortex (PFC) (bilateral frontal superior medial gyrus, left middle frontal gyrus and left mid-orbitofrontal cortex), motor regions (bilateral pre-supplementary area), left middle temporal gyrus, parietal cortex (left inferior and superior giri) and bilateral putamen. Compared to PD non-ICD, PD-ICD patients showed enhanced activation in left inferior parietal cortex, right precuneus and bilateral putamen. Time course analyses revealed a Group by Condition interaction in the left and right insula, and right inferior frontal gyrus, where PD-ICD patients had lower activation in the mixed feedback condition than the other groups. Group differences in functional connectivity with the striatum were observed. Relative to HC, PD-ICD patients had stronger coupling with the bilateral dorsolateral PFC, and PD non-ICD patients had stronger connectivity with the orbitofrontal cortex/ventromedial PFC.
Conclusions. PD-ICD patients show altered activation of the cortex (insula and inferior frontal gyrus) and abnormal functional connectivity (striatum-PFC regions) in structures involved in risk and uncertainty during reward-based decision-making. Differences in the response to mixed feedback decision could be associated with a difficulty of acquisition of probabilistic contingencies in the learning phase in comparison to a non ICD population.

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Poster

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Title: Firing rate and proportion of subthalamic oscillatory neurons increase associatd with Parkinson's disease progression

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Abstract: Objective To explore whether neuronal firing rate and proportion of oscillatory neuronal activity in the subthalamic nucleus (STN) is associated with severity in patients with Parkinson's disease (PD). **Methods** Twenty-two patients (M:9, F:13) with Parkinson's disease who received subthalamic deep brain stimulation treatment were included. Microelectrode recording was performed in the STN. Single unit analysis including interspike interval (ISI) was used to study neuronal firing rate and patterns. Power spectral analysis was used to evaluate neuronal oscillation. Clinical outcome was assessed using Unified Parkinson's Disease Rating Scales (UPDRS III) pre-and post-surgery. The groups of the early-stage and the advanced-stage were defined based on the UPDRS III scores, disease duration and the side of initial symptoms. **Results** Of total 163 neurons identified from 32 STN, there were 66 neurons with mean firing rate of 46.2±13.6 Hz obtained from the patients in the early-stage group whereas 97 neurons with mean firing rate of 59.9±17.1 Hz were obtained from patients in the advanced-stage group. Power spectral analysis showed that there were 27 (40.9%) oscillatory neurons identified from the STN neurons in the early-stage patient group (n=66) whereas 55 (56.7%) oscillatory neurons were identified from the STN neurons in the advanced-stage patient group (n=95). Further analysis found that 29.7% (8/27) ß oscillatory neurons were observed in the early-stage group whereas 52.7% (29/55) ß oscillatory neurons were observed in the advanced-stage group. When comparing the mean firing rate and proportion of oscillatory neurons in the STN of early-stage group with that of neurons in the STN of advanced-stage group, it was found that there was a 29. 6% increase STN mean firing rate of neurons (46.2±13.6 Hz vs. 59.9±17.1 Hz, $P<0.05$) and a 36.8% increase proportion of oscillatory neurons (40.9% vs. 56.7%) between the two groups. In particular, a 77.7% increase proportion of ß oscillatory neurons was obtained between the early-stage and advanced-stage groups (29.7% vs.52.8%, $P<0.01$). **Conclusions** The results strongly suggest that both subthalamic nucleus neuronal firing rate and proportion of ß oscillatory neurons increase with PD progression.

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Poster

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Title: Visual tracking abnormalities in hemisphere-asymmetric Parkinson's disease

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Abstract: Parkinson's disease (PD) usually has a hemispheric asymmetry of neurodegeneration, clinically manifested as one side of the body being more affected than the other. It has been proposed that the right hemisphere is superior to the left in oculomotor control and thus PD patients with right hemisphere neurodegeneration should theoretically have more severe oculomotor abnormalities than patients with left hemisphere neurodegeneration. However, little research has studied this question and the reported limited results are inconsistent. In current study, we used a visual tracking task (Liston & Stone, 2014) to examine whether and how hemispheric asymmetry in PD affects general visual tracking ability. Specifically, participants visually tracked step-ramp target motion that varied unpredictably from trial to trial (speed: 16°/s-24°/s; direction: 0°-360°) to minimize the expectation effect. The task took a reasonably short time to finish (less than 15 minutes) but can evaluate many independent aspects of eye tracking ability (e.g., initial pursuit latency, initial pursuit acceleration, steady-state pursuit gain, & proportion of smooth pursuit vs. saccadic tracking). We tested 27 idiopathic patients with hemisphere-asymmetric PD ON medication and 21 demographically-matched healthy controls. In 13 patients, the motor symptoms were predominant on the left side of the body reflecting right-hemispheric neurodegeneration (LPD); in 14 patients, the motor symptoms were predominant on the right side of the body reflecting left-hemispheric neurodegeneration (RPD). LPD and RPD patients were demographically matched and had similar cognitive abilities and degree of motor-symptom asymmetry. The two patient groups also contained a matched number of akinetic-rigid and tremor-dominant patients. We found that RPD patients did not differ from healthy controls in their visual tracking performance. However, LPD patients displayed larger initial pursuit latency, smaller initial pursuit acceleration, lower steady-state pursuit gain and smaller proportion of smooth pursuit tracking than did healthy controls, indicating that visual tracking abnormality is specific to LPD patients with right-hemispheric neurodegeneration. Our study is the first study that systematically examined how hemispheric asymmetry of neurodegeneration influences visual tracking ability in PD. Our results are in line with previous findings that unilateral hemispheric lesions can cause asymmetrical oculomotor abnormalities for both smooth pursuit and saccadic eye movements, and that neurodegenerative symptoms can be tracked with oculomotor methods.

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Title: Neural correlates of impaired motor timing processing during speech production and hand movement in Parkinson’s disease

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Abstract: Patients with Parkinson’s disease (PD) demonstrate impairments in temporal processing aspects of motor function, which can affect their speech and hand movement reaction time. However, the underlying neural bases of such motor timing impairment in PD has remained unclear. Previous studies in neurotypical healthy adults have demonstrated that temporal predictability of sensory cues were associated with attenuated neural activities during the preparatory phase of movement initiation and inhibition for speech production and hand movement, leading to improved motor reaction time. This effect was explored by examining the suppression of premotor event-related potentials (ERPs) elicited prior to the onset of speech and hand movement initiation and inhibition in response to temporally predictable vs. unpredictable sensory stimuli. This evidence supports the notion that the timing aspects of sensory stimuli can modulate neural processing of motor responses in speech and hand modalities. In this study, we investigated neural activities prior to the onset of speech and hand movement in response to temporally-predictable and unpredictable sensory stimuli in patients with PD and a healthy age-matched control group. Event-related potentials (ERPs) were recorded in 15 PD patients and 15 control subjects while they were visually-cued to prepare to produce a steady vocalization of a vowel sound (speech task) or press a button (hand movement task) in a randomized order, and to initiate the cued movement following the onset of a circle on the screen (go signal) and inhibit ongoing movement after the circle disappeared (stop signal). We found that the motor reaction times for speech and hand movement initiation and inhibition were significantly slower in PD patients compared with control subjects. In addition, analysis of ERP responses for control subjects revealed that the premotor neural activities (time window: -100 to 0 ms) over the frontal and parietal areas were significantly suppressed in response to temporally-predictable sensory cues before speech and hand movement initiation and inhibition. However, the suppression of premotor ERPs were not observed in PD Patients in response to temporally-predictable stimuli, suggesting the impairment of motor timing processing in PD patients. These findings implicate

the role of basal ganglia in temporal information processing during movement. Based on these results, we argue that the PD patients suffer from motor timing deficits that impair their ability to extract temporal information from external sensory cues for driving motor responses for speech and hand movement initiation and inhibition.

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Poster

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Topic: C.03. Parkinson’s Disease

Title: Low-frequency oscillations in postural sway vary with sensory weighting and scale with fall-risk in Parkinson's disease

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Abstract: Studies have demonstrated that aging, visuomotor processing and neurological disease (e.g. stroke and cerebellar ataxia) influence oscillations from 0-1 Hz in isometric force contractions. However, these effects have not been studied in postural control, which is necessary for maintaining balance and preventing falls. Therefore, the purpose of this study was to investigate the effects of sensory weighting on low-frequency oscillations in postural sway, and their implications for fall-risk in people with Parkinson’s disease. 70 Parkinson’s disease patients (69.5 ± 8.1 yrs, 22 females), 38 older adults (68.8 ± 8.5 yrs; 16 females) and 21 young adults (19.1 ± 0.9 yrs; 9 females) volunteered to participate in this study. All subjects performed a static balance assessment using a portable force plate. Sensory weighting was examined by having subjects maintain quiet unperturbed standing with both eyes closed and eyes open over six 20-s trials. Parkinson’s disease patients were further sub-grouped based on average COP excursions during the eyes closed trials into high- (>38 cm) and low (<38 cm) fall-risk groups. Changes in low-frequency oscillations were quantified by examining the absolute wavelet power in nine frequency bins from 0-1.08Hz at every 0.12 Hz. We find that low frequency oscillation in postural sway increase with removal of visual feedback and increase with increasing fall-risk. Furthermore, Parkinson’s disease patients at high fall-risk are highly dependent on vision for postural control when compared with healthy controls and PD patients at low risk for falls.

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Poster

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Topic: C.03. Parkinson's Disease

Title: Correlation between electroencephalogram and electromyogram in parkinson's disease: A review

Authors: *A. SAIKIA, V. K. PANDEY, S. PAUL
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Abstract: The main of this study is to correlate the Electroencephalogram (EEG) and Electromyogram (EMG) in Parkinson's disease patients. It will be a true scientific validation tool to justify the clinical and mathematical correlation between two of the biophysical parameters. Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder with a multi-factorial etiology. The pathological hallmarks of Parkinson's disease (PD) are marked loss of dopaminergic neurons in the substantianigra pars compacta (SNc), which causes dopamine depletion in the striatum, and the presence of intracytoplasmic inclusions known as Lewy bodies in the remaining cells. It remains unclear why dopaminergic neuronal cell death and Lewy body formation occur in PD. The pathological changes in PD are seen not only in the SNc but also in the locus coeruleus, pedunculo pontine nucleus, raphe nucleus, dorsal motor nucleus of the vagal nerve, olfactory bulb, parasympathetic as well as sympathetic post-ganglionic neurons, Mynert nucleus, and the cerebral cortex. It will be a novel scientific validation to correlate between EMG and EEG in Parkinson' Disease patients. EMG is the electrical potential that is caused by the function of muscles. EMG signal can be measured from muscles by using needle electrodes or surface electrodes attached to the skin surface which is known as surface EMG measurement. The traditional methods to analyze surface EMG signals are mainly based on amplitude and spectral analysis which are mainly used to measure level of muscle activation and fatigue. The advantage of using EMG in the assessment of PD is its objectivity and quantitativeness to evaluate the motor function. Neurophysiological measurements may help in the near future in advancing the diagnosis and in the differential diagnosis of PD. EEG is one of the oldest methods for studying brain function. It has been proposed as a promising mathematical tool for the detection of cognitive decline in neurodegenerative disorders including PD.

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Topic: C.03. Parkinson's Disease

Title: The effect of Parkinson's disease on multisensory temporal integration

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Abstract: Multisensory integration is crucial to perceptual understanding, but cues from multiple sensory modalities do not necessarily arrive at the brain simultaneously. The window of time over which sensory inputs can be separated in time but still interpreted as simultaneous is termed the "temporal binding window" (TBW). Extended TBW of auditory and visual stimulus combinations can be associated with dyslexia, schizophrenia, and even obesity, raising the possibility it may a contributing pathologic factor in these conditions. Parkinson's disease (PD) is known to affect unimodal temporal discrimination, but its relationship to the perceptual timing of multisensory events is not known. To examine the relationship between PD and temporal binding, 8 individuals with PD for a minimum of 2 years and 25 healthy controls without cognitive, auditory, or visual impairments were presented with video + audio stimuli of a hammer striking a board, or a speaker saying "Ba." Audiovisual asynchrony varied in 10 msec increments. Two-down, one-up interleaved staircase procedures (71% correct psychometric response) were used for stimuli going from perfectly in-sync (0 msec offset) to out-of sync and vice-versa. Temporal binding window was defined as the average of the 71% correct values on the staircases in each direction. An extended temporal binding window was apparent in the PD cohort for both stimulus types (mean±std: 573±71 msec for speech and 539±154 msec for hammer) as compared to healthy controls (mean±std: 467±146, 411±137 msec for speech and hammer, respectively). The control cohort did not exhibit an age effect (r=0.145), however, PD temporal binding was strongly related to the duration of PD (r=0.734). These results demonstrate that PD disrupts temporal regulation and that this effect correlates with disease duration. Widening of the TBW may make it difficult for patients to perform tasks, such as walking, that involve multimodal perception and are commonly disturbed in PD. Given that TBW can be narrowed through perceptual training, these data may offer a therapeutic intervention to help ameliorate symptoms in PD.

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Poster

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Title: Abnormal characteristics of physiological network in patients with idiopathic REM sleep disorder during REM sleep

Authors: *S. HEO[1], D. YEO[1], P. SEO[1], H. KIM[1], K. CHA[1], J. CHOI[1], K.-Y. JUNG[2], K. KIM[1]
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Abstract: Rapid-eye movement (REM) sleep behavior disorder (RBD) is a sleep disorder characterized by dream enactment behavior (DEB) and the loss of muscle atonia during REM sleep (RSWA). In this study, we performed multiple physiological signal analysis using time delay stability (TDS) methods in patients with idiopathic RBD (iRBD) and healthy controls during sleep, in order to investigate the abnormal characteristics of physiological network associated with iRBD.
11 drug-naïve idiopathic RBD patients (age: 66.36±6.73 years, F: 2, M: 9) and 10 healthy controls (age: 62.30±7.45 years, F: 3, M: 7) participated in the experiment. 21-channel EEG, electrooculography (EOG), electromyography (EMG), electrocardiography (ECG) and respiration signal were recorded during one overnight sleep. Artifact-free 30-second epochs of the signals were extracted at each sleep stage. The physiological signals were converted to characteristic value time-series that represent the physiological activities of the brain (alpha, beta, sigma, theta, and delta subbands), eye, arm, leg, heart, and respiration. The TDS was calculated to quantify the coupling between physiological time-series. Statistical comparisons between iRBD patients and controls were performed using independent t-test and FDR correction for multiple comparisons. The correlation between the TDS and clinical measures was investigated by Pearson’s correlation coefficient.
The TDSs were significantly increased in the RBD patients compared to the controls during REM sleep for delta-alpha, delta-sigma, delta-beta, theta-alpha, theta-sigma, theta-beta, delta-HR and beta-eye couplings ($t<-3.3$, $FDR<0.02$). The delta-alpha coupling was significantly anti-correlated with Korean version of the sniffin’ sticks test (KVSS) score, which is known as a

good index of the severity of neurodegenerative disease, in only RBD patients (r=-0.837, p=0.001). Also, significant anti-correlation was observed between TDS of delta-HR coupling and the KVSS (r=-0.816, p=0.002).
The increments of delta-HR coupling, which is anticipated to be related to sleep control mechanisms, can be reflects a cardiac autonomic dysfunction in RBD patients. The abnormally increased TDSs during only REM sleep could be may be related to abnormal characteristics of RBD such as DEB and RSWA. We found abnormal characteristics of physiological network associated with RBD.

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Title: Global and local oscillatory changes associated with pallidal deep brain stimulation in Parkinson disease

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Abstract: Parkinson disease (PD) is a neurodegenerative disorder of central nervous system that affects motor function. Abnormal neural beta oscillatory activity has been observed in the subthalamus nucleus (STN) and Globus Pallidus internus (GPi) of patients with PD. Deep brain stimulation (DBS) of GPi has been shown in randomized clinical trials to manage PD symptoms. Despite its documented clinical efficacy, the underlying mechanisms of GPi-DBS, within regions and across regions, is still not well understood. In this study, we hypothesize that GPi-DBS may

reduce the hyper-synchrony oscillatory pattern in patients with PD. To do so, we explore the effect of DBS on both local and global oscillatory activity. Seven patients with PD underwent GPi-DBS implantation. Intraoperative recordings of GPi local field potentials (LFPs) and ipsilateral motor cortex electrocorticography (ECoG) were obtained in two modes of on and off GPi stimulation. To investigate the subcortical-cortical phase synchrony relationships, before and during DBS, phase lag index (PLI) was used. Power spectrum analysis was done at both subcortical and cortical levels to explore the effect of DBS on the local oscillatory activity. The sub-beta analysis was performed in low beta (13-20 Hz) and high beta (21-35 Hz) frequency bands separately. All the cortical analysis was mainly limited to three major areas of premotor, primary motor, and sensorimotor cortex. Spearman correlation coefficient was calculated to obtain the relationships between the DBS related symptom improvement, during DBS, and the neural phase synchrony changes. The phase analysis showed significant subcortical-cortical synchrony reduction (Wilcoxon signed rank test, p-value<0.016) particular to the primary motor cortex during DBS in the high beta band. No statistical subcortical-cortical phase synchrony difference was observed at the premotor and sensorimotor sites between two conditions. The local spectral analysis did not show any significant changes in the beta (and the sub-bands) at GPi and cortical level. We observed a positive correlation (R=0.35) between pallidal-M1 phase synchrony changes and the clinical score improvement during DBS. These findings suggest suppression of pallidocortical high beta coupling may be a critical therapeutic mechanism of GPi DBS. An exaggerated pallidocortical high beta coupling may, therefore, be a critical pathophysiological underpinning of PD. A better understanding of the DBS mechanisms on the alleviation of PD symptoms can contribute to the development of closed-loop DBS in which the patients' neurophysiological parameters will be considered in optimizing the DBS parameters.

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Title: Multimodal fMRI investigation of reward-driven behaviors in Parkinson's disease

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Abstract: Impulse-control disorders (ICDs) in Parkinson's disease (PD) are associated with the use of non-ergot dopamine agonist (DAA) drugs, which preferentially target D2/D3-type dopamine receptors. ICDs vary in manifestation, but center around compulsive participation in reward-driven activities. We aim to identify regional changes in brain activity related to both short-term response to DAA and network activity patterns distinguishing ICD-sensitive and ICD-resistant individuals.
PD patients (n=37; gender=12F/25M; age=61.8±8.4 years) were recruited from the clinic, and classified as ICD+ or ICD- based on a semi-structured clinical interview. Pseudo-continuous arterial spin labeling (TR/TE=4000/11ms, post-labeling delay=1500ms) was used to quantify cerebral blood flow as a measure of regional metabolic activity, while blood oxygenation level-dependent fMRI (TR/TE=2000/35ms) was employed to examine resting state functional connectivity effects. This scan protocol was applied both On-DAA (but not levodopa) and Off-dopamine therapy. Acute metabolic DAA response was defined as percent change in blood flow from Off-dopamine to On-DAA state. We hypothesized that (1) PD patients with ICDs would exhibit greater responses to DAA administration than patients without ICDs in mesocortical and mesolimbic circuit components, especially the ventral striatum; and (2) that these networks would exhibit increased temporal synchrony in ICD+ patients when On-DAA, but not in ICD- patients.
Blood flow response to acute DAA in the ventral striatum was significantly greater in ICD+ than ICD- patients ($p=0.03$). No other tested subcortical regions exhibited significant differences between groups. Functional connectivity between the ventral striatum and anterior cingulate gyrus ($p=0.03$), globus pallidus ($p=0.02$), thalamus ($p=0.02$), and putamen ($p=0.01$) was significantly greater in the ICD+ group. No direct effect of DAA administration on connectivity was identified, although DAA and ICD group status interacted to increase connectivity between amygdala and midbrain ($p<0.01$).
We found that, in the ventral striatum, PD patients with ICDs exhibit both an elevated acute metabolic response to DAAs, and greater connectivity with mesocorticolimbic circuits. We conclude that enhanced DAA activation of ventral striatal dopamine receptors, especially D3-type receptors, is likely important in sensitizing a subset of PD patients to reward-driven behaviors.

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Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.01/W9

Topic: C.05. Neuromuscular Diseases

Support: NIH SBIR Grant 1R43NS097080-01A1

Title: Use of iPSC-derived human motor neurons in high-throughput phenotypic screening

Authors: *M. L. HENDRICKSON[1], J. KOUZNETSOVA[2], W. ZHENG[2], Z.-W. DU[1]
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Abstract: There exists a dire need for more effective drugs to treat disorders of the central nervous system (CNS), and new cell culture models that are more relevant to psychiatric and neurological diseases are needed to improve the success rate of drug development programs. One such approach is the use of neurons differentiated from patient induced pluripotent stem cells (iPSCs), which present new opportunities for modeling disease processes and screening drug libraries. We have developed technology to produce very large quantities of highly enriched human neurons from patient iPSCs and to greatly accelerate their maturation. We subsequently developed two high-throughput screening (HTS) systems using human motor neurons derived from individuals with amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA). Using genome editing techniques on the iPSC lines, the reporter nanoluciferase (NLuc) was fused to endogenous neurofilament light chain (NF-L) for ALS and full-length SMN2 for SMA. Nanoluciferase is more sensitive than the traditional luciferase and allows for a simple and quantitative readout of NF-L and SMN2 protein levels. The assays were adapted to meet HTS requirements, including: large batch sizes, 1536-well format, minimal well-to-well variation, short-term culture, plating by automated dispenser, and low reagent volumes. Applying a quantitative HTS approach, we screened the LOPAC, NPC, and MIPE libraries (>6,000 compounds) in a dose dependent manner on both motor neuron lines with a hit rate of ~0.5%. This work demonstrates the feasibility of running HTS campaigns using human neurons, which present a more physiologically relevant drug discovery platform.

Disclosures: **M.L. Hendrickson:** A. Employment/Salary (full or part-time):; BrainXell, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainXell, Inc.. **J. Kouznetsova:** None. **W. Zheng:** None. **Z. Du:** A. Employment/Salary (full or part-time):; BrainXell, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainXell, Inc..

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.02/W10

Topic: C.05. Neuromuscular Diseases

Support: TEDCO 2014-MSCRFI-0715

Title: Genetic and functional comparison of hESCs- and iPSC-derived Schwann cells

Authors: *R. MI, J. EHMSEN, Q. SHI, B. MUKHERJEE-CLAVIN, G. LEE, A. HOKE
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Abstract: Injury to the peripheral nervous system (PNS) results in significant morbidity and affects quality of life. Although the PNS can regenerate in adult mammals, functional recovery is relatively poor in humans especially after proximal nerve lesions. This is primarily due to atrophic changes in chronically denervated Schwann cells in the distal nerves. Transplanted primary Schwann cells can replace/supplant atrophic host Schwann cells in the distal nerves, but human embryonic stem cell- (hESC) or human induced pluripotent stem cell- (hiPSC) derived Schwann cells offer greater potential for future therapeutic interventions. However, differentiation potential and impact on functional recovery of hESC- versus hiPSC-derived Schwann cells is unknown.

In order to explore whether Schwann cells derived from hESCs and hiPSCs are comparable to each other in terms of gene expression after differentiation under identical protocols, we performed RNA-seq profiling of CD49d positive cells (Schwann cells) derived from three HESCs (H1, H7 and H9) and three hiPSCs (GM08398, GM02623 and GM01582). For Schwann cell differentiation, hESCs or hiPSCs were maintained and differentiated according to the protocol developed in the Lee lab, and purified by FACS using an antibody against CD49d. We validated Schwann cell identity by immunocytochemistry using known Schwann cell markers. CD49d-positive differentiated cells were positive for GFAP, s100B and p75. RNA-seq analysis identified only 105 differentially expressed genes between hESC-derived and hiPSC-derived Schwann cell lines, out of nearly 40,000 transcripts (~0.27%). For those genes that appeared to be differentially expressed, ~40% and ~20% showed very low expression in the hESC-derived and hiPSC-derived Schwann cell lines, respectively. Similarly, only 290 out of nearly 60,000 isoforms were differentially expressed between the cell lines (~0.49%).

These results indicate substantial genetic similarity between the hESC- and hiPSC-derived Schwann cell lines. Ongoing experiments to assess the myelination potential of these hESC- and hiPSC-derived Schwann cells *in vitro* and *in vivo* include co-culture experiments using GFP labeled hESC- and hiPSC-derived Schwann cells with rat primary dorsal root ganglion (DRG) neurons, and transplantation into two peripheral nerve injury models focusing on chronic nerve

injury to mimic human disease. If myelination potential is confirmed in *vivo*, these hESC- or hiPSC-derived Schwann cells may prove useful for future human clinical trials.

Disclosures: R. Mi: None. **J. Ehmsen:** None. **Q. Shi:** None. **B. Mukherjee-Clavin:** None. **G. Lee:** None. **A. Hoke:** None.

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.03/W11

Topic: C.05. Neuromuscular Diseases

Support: The ALS Association ID:15-IIP-199

The ALS Association ID: 17-LGCA-329

Title: V-Smart™ Nanomedicine for the Treatment of ALS (LAUR-301): Non-Invasive Targeted Delivery of GDNF to Degenerating Motoneurons in ALS

Authors: *I. HOLLANDER[1], M. POPOV[1], E. SHAUBI[1,2], A. ARMOZA[1], J. MILAM[1], E. HARLEV[1], V. KAS'YANOV[1], C. LINDER[1,2], E. HELDMAN[1,2]
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Abstract: Lauren Sciences has developed the novel V-Smart™ nanovesicle platform (comprised of its novel proprietary bolaamphiphiles) for targeted drug delivery. V-Smart™ can encapsulate non-brain penetrant therapeutic agents, cross the blood-brain barrier (BBB) following systemic administration, target specific sites in the central nervous system (CNS) and selectively release the encapsulated therapeutic agents at target sites.
Based on its V-Smart™ technology, Lauren Sciences successfully designed a V-Smart™ Nanomedicine for the treatment of ALS -- LAUR-301. LAUR-301 is customized to encapsulate glial cell line-derived neurotrophic factor (GDNF), and engineered to deliver the encapsulated GDNF to the CNS, target the encapsulated GDNF to regions in the CNS where motoneuron degeneration occurs in ALS patients and selectively release the GDNF at its site of action. GDNF has shown beneficial effects, by preventing motoneuron degeneration, in preclinical studies of ALS mouse models. However, GDNF does not penetrate the BBB, is susceptible to proteases, does not diffuse well from direct application sites in the CNS (due to tight binding to components of the extracellular matrix) and causes adverse effects at high local concentrations. LAUR-301 solves these problems, as LAUR-301 is administered systemically, delivers GDNF to the CNS while encapsulated, and distributes GDNF to its targeted action sites without producing high local concentrations (unlike direct application to the CNS), thus, enabling the GDNF to potentially provide an effective therapy for ALS.

Here, the data presented shows that LAUR-301: (1) selectively targets cultured cells known to accumulate at CNS regions where ALS motoneuron degeneration occurs; (2) efficiently encapsulates GDNF while maintaining its activity; and (3) delivers, in a dose dependent manner, significant amounts of GDNF into brain and spinal cord of wild type mice, after i.v. administration, without toxicity.
Next, Lauren Sciences plans to prove that, after systemic administration, LAUR-301: (1) delivers GDNF into brain and spinal cord of ALS mice and distributes it to regions of motoneuron degeneration; (2) is effective in treating ALS mice, by disease modification (slowing or reversing neurodegeneration) and extension of life span. Therapeutic efficacy in ALS mice will facilitate IND enabling studies and provide strong rationale for clinical trials.
The goal is for LAUR-301 to be a transformative V-Smart™ Nanomedicine that protects against neurodegeneration, and induces neurorestoration, in ALS patients. LAUR-301 success can also pave the way for development of other V-Smart™ Nanomedicines for ALS.

Disclosures: I. Hollander: A. Employment/Salary (full or part-time):; Lauren Sciences LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lauren Sciences LLC. **M. Popov:** A. Employment/Salary (full or part-time):; Lauren Sciences LLC. **E. Shaubi:** A. Employment/Salary (full or part-time):; Lauren Sciences LLC. **A. Armoza:** A. Employment/Salary (full or part-time):; Lauren Sciences LLC. **J. Milam:** A. Employment/Salary (full or part-time):; Lauren Sciences LLC. **E. Harlev:** A. Employment/Salary (full or part-time):; Lauren Sciences LLC. **V. Kas'yanov:** A. Employment/Salary (full or part-time):; Lauren Sciences LLC. **C. Linder:** A. Employment/Salary (full or part-time):; Lauren Sciences LLC. **E. Heldman:** A. Employment/Salary (full or part-time):; Lauren Sciences LLC.

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.04/W12

Topic: C.05. Neuromuscular Diseases

Title: Occipital nerve stimulation for the treatment of refractory occipital neuralgia: a case series

Authors: *A. DIAZ, O. P. KEIFER, Jr, M. C. CAMPBELL, Y. B. BEZCHLIBNYK, N. M. BOULIS
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Abstract: Occipital neuralgia (ON) is a debilitating cranial neuropathy that is associated with lancinating pain within the distribution of the greater (~90%), lesser (~10), and/or third occipital nerves (rare). It is a relatively understudied entity, and, thus, there is limited epidemiological data on incidence, prevalence, or predisposing risk factors. As of yet, there is no clear standard of care

and many of the treatment options for occipital neuralgia are under active investigation. Occipital nerve stimulation (ONS) has been reported in limited studies (mean of 9-10 patients) for the treatment of medically refractory cases of occipital neuralgia. The appeal of ONS lies in its reversible nature and ability to provide a trial stimulation period to assess efficacy. In a partial readdress, we present a retrospective case series analysis on the use of ONS for ON in 20 patients. A total of 29 patients were evaluated at the Emory Neurosurgery Clinic. Of those 20 (69%) were naïve to ONS treatment, underwent a trial and then permanent implantation of the system. The analysis of patient outcomes was based on pre- and post-operative pain score comparisons using a paired t-test. The majority of patients had unilateral ON, with both a constant and lancinating pain component. The average reported pain scores were quite elevated at 7.4, with the average maximum reported pain-score at 8. These patients failed an average of 7 drugs of various classes and the average follow-up time was 410 days. Of the patients selected for ONS trial stimulation 75% (20 of 25) went onto full implantation of the system. Of these patients, 85% self-reported an improvement of greater than 50% pain reduction. This is corroborated by a significant reduction in the average reported pain score of 7.4 pre-operatively to 2.9 during post-operative follow-up (paired t-test, $P<0.005$). The results of the study suggest that ONS is a feasible treatment option for long term control of the symptoms of ONS. With an increasing interest in occipital neuralgia in neurology and neurosurgery, it is hoped that future work will focus on long-term prospective studies.

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Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.05/W13

Topic: C.05. Neuromuscular Diseases

Support: NS079348

Title: Chronic intermittent mild whole-body hypothermia is therapeutic in a mouse model of ALS

Authors: *L. J. MARTIN, M. WONG
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Abstract: Therapeutic hypothermia (targeted temperature management) is the standard of care for neonatal hypoxic-ischemia encephalopathy and adult cardiac arrest and is being tested for the treatment of CNS trauma. The possibility that therapeutic hypothermia has applications in chronic neurodegeneration has not been examined, despite the likelihood that mechanisms of

acute and chronic neurologic injury may have some commonalities. We tested the hypothesis that chronic, intermittent, whole-body, mild hypothermia has therapeutic efficacy in a mouse model of amyotrophic lateral sclerosis (ALS). Transgenic mice expressing high levels of human mutant superoxide dismutase-1 (hSOD1-G93A variant) were used. Male and female mice culled from several litters were randomly assigned to groups receiving euthermia/normothermia (NT, n=25) or therapeutic hypothermia (HT, n=25) initiated at early symptomatic stages of disease. The HT protocol was whole-body mild cooling (1-3 ^{0}C) of freely moving mice in a cooling chamber for 12 hours on alternate days. Body temperature was monitored rectally, orally, and axillary. Mice underwent spontaneous rewarming when removed from the cooling chamber. NT mice were maintained at room temperature (37 ^{0}C). HT significantly ($p < 0.05$) reversed and attenuated functional decline on a motor test (running wheel) and significantly ($p < 0.05$) extended lifespan of hSOD1-G93A mice. Effects appeared greater in female mice. HT was associated with significantly ($p < 0.05$) elevated levels of tissue mitochondrial uncoupling protein 3, heat-shock protein, and protein sumoylation, motor neuron protection, and decreased mitochondrial pathology and inflammatory reaction during the disease process. This work demonstrates that targeted temperature management and rewarming may have application in chronic neurodegenerative disorders as well as in acute neurological injury. We show in a preclinical mouse model of ALS that longitudinal intermittent HT has therapeutic effects on neurologic and pathologic outcomes that may be relevant clinically for human chronic neurodegenerative disorders.

Disclosures: L.J. Martin: None. **M. Wong:** None.

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.06/DP03/W14 (Dynamic Poster)

Topic: C.05. Neuromuscular Diseases

Support: The Stanford Innovation Fund

Takeda Pharmaceuticals' Science Frontier Fund

P30 NS069375 06

Title: Drp1 hyperactivation in ALS

Authors: A. U. JOSHI[1], A. D. CUNNINGHAM[1], N. L. SAW[2], M. SHAMLOO[2], *D. MOCHLY-ROSEN[1]
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Abstract: Mitochondrial dysfunction, bioenergetic failure, and oxidative stress are common pathological hallmarks of amyotrophic lateral sclerosis (ALS). However, there is a limited understanding of the exact mechanisms underlying the molecular events leading to the disease progression. One of the reported contributors to ALS pathology is mitochondrial dysfunction associated with excessive mitochondrial fission and fragmentation. Excessive mitochondrial fragmentation is a process mediated, at least in part, by Drp1 hyperactivation. Here we examined the hypothesis that mitochondrial dysfunction is due to Drp1 hyperactivity and mitochondrial excessive fission and fragmentation in ALS. To that end, we determined whether pharmacological inhibition of Drp1/Fis1 interaction with P110 affects disease progression. We observed mitochondrial excessive fragmentation and dysfunction in several familial forms of ALS patient-derived fibroblasts as well as in cultured motor neurons expressing SOD1 mutant. In both patient-derived cells and in the rodent cell model, inhibition of Drp1/Fis1 interaction by a selective peptide inhibitor, P110, led to a significant reduction in mitochondrial reactive oxygen species levels, and to improvement in mitochondrial structure and functions. We then treated mice expressing G93A SOD1 mutation (a mouse model of ALS) with P110. Sustained treatment, beginning at the symptomatic phase of the disease starting at the age of 90 days, correlated with decreased Drp1 association with the mitochondria in the spinal cord and produced an improvement in motor performance and survival. Together, these data suggest that inhibitors of Drp1 hyperactivation, such as P110, may be an attractive therapeutic approach for ALS patients.

Disclosures: A.U. Joshi: None. **A.D. Cunningham:** None. **N.L. Saw:** None. **M. Shamloo:** None. **D. Mochly-Rosen:** None.

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.07/W15

Topic: C.05. Neuromuscular Diseases

Support: R01 NS095969

Title: Splicing repression is a major function of TDP-43 in motor neurons: Identification of a novel therapeutic strategy for ALS/FTD

Authors: *A. N. DONDE[1], J. P. LING[2], K. E. BRAUNSTEIN[3], M. SUN[5], L. CHEN[2], P. C. WONG[4]
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Abstract: In sporadic amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), Tar DNA-binding protein 43 (TDP-43), a conserved RNA-binding protein (RBP), clears from the nucleus and forms cytoplasmic inclusions, a pathological hallmark thought to be central to disease pathogenesis. While evidence supports the notion that nuclear depletion of TDP-43 underlies cytotoxicity, the precise mechanism is unknown.
We discovered that TDP-43, a founding member of a new class of RBPs, represses the splicing of non-conserved cryptic exons by binding to simple microsatellite repeats, a function compromised in ALS patients. Depletion of TDP-43 leads to incorporation of cryptic exons that usually alters the proteome of affected cells. Because several putative roles have been attributed to TDP-43, it will be critical to establish first that this splicing repression is a major role of TDP-43 in motor neurons. We initially showed that cryptic exons can be repressed in TDP-43 deficient cells using a chimeric protein consisting of the N-terminal RNA-recognition domain of TDP-43 fused with an unrelated but well-known splicing repressor (RAVER1), indicating that TDP-43 splicing repression is its major role in replicating cells. To establish this in post-mitotic mammalian motor neurons *in vivo*, we used a mouse model lacking Tdp-43 in lower motor neurons that exhibits age-dependent motor neuron disease. As predicted, incorporation of cryptic exons occurred in the spinal cords of these knockout mice.
We then delivered our chimeric construct in neonatal mice using an AAV9 viral vector, maintaining long-term expression in 55-70% of lower motor neurons without overt toxicity. Treated conditional Tdp-43 knockout mice showed a delayed onset, attenuated progression of motor symptoms as measured by hanging wire rotarod tests, and extended lifespan. Transcriptome analysis of FACS-isolated Tdp-43 deficient motor neurons from mice treated with our chimeric construct showed the extent of splicing re-suppression. Our findings establish that splicing repression is a major role of TDP-43 in mammalian motor neurons and support the idea that the inability to repress TDP-43 splicing is a major pathogenic mechanism underlying TDP-43 pathology, pointing to a promising AAV9 therapeutic strategy for ALS/FTD.

Disclosures: **A.N. Donde:** None. **J.P. Ling:** None. **K.E. Braunstein:** None. **M. Sun:** None. **L. Chen:** None. **P.C. Wong:** None.

Poster

670. Motor Neuron Disease: Therapeutics

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.08/W16

Topic: C.05. Neuromuscular Diseases

Support: Funded by Prosetta

Title: Small molecules targeting catalytic multiprotein complexes that misassemble TDP43 in ALS

Authors: S. TROSSBACH[1], S. SELVARAJAH[2], S. SAHU[2], I. SOLVIEV[2], N. DEYARMAN[2], V. BADER[1], S. JACOBSEN[3], N. BRANDON[3], K. PAULVANNAN[2], V. ASUNDI[2], D. DEY[2], *C. KORTH[1], V. R. LINGAPPA[2]
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Abstract: Background: Our working hypothesis is that multiprotein complexes (MPCs) are not formed spontaneously, but rather are catalytically assembled by other transient and highly dynamic MPCs, which we term assembly machines. We hypothesize that pathological protein aggregation is the result of aberrant assembly machine function occurring upstream in the relevant biochemical pathway. If small molecules binding to allosteric sites that normalize assembly machine composition and function could be found, they should be efficacious against particular protein aggregation diseases We have identified 300 small molecule chemotypes, termed the Hit-finder Collection, that are active against a diverse array of assembly machines commandeered by viruses for their capsid formation. These have served as an effective starting point for specific assembly machine-modulating drug development.
Objective: Identify hit-finder compounds active against TDP-43 aggregation in ALS.
Methods: Induction of stress granule formation and cytosolic TDP-43 accumulation were performed by treating SH-SY5Y cells with sodium arsenite, a cellular model for ALS. We developed a novel biochemical assay allowing us to directly assess drug action on cytoplasmic TDP-43 mislocalization, aggregation and association to stress granules. This assay involved a combination of *in vitro* crosslinking, low salt protein extraction and gradient ultracentrifugation. The potency of the Hit-finder Collection to correct TDP-43 pathology was screened by an immunocytochemistry (ICC) approach and the best chemotypes were more intensely investigated by the biochemical assay, drug resin affinity chromatography, and a C.*elegans* swimming-induced paralysis animal model.
Results: Three lead series correcting cellular TDP-43 pathology were identified. Analogs were shown to have a robust structure-activity-relationship. Drug resin affinity chromatography (DRAC) was used to identify distinctive MPCs for each chemotype each containing different protein previously implicated in ALS.
Conclusion: Three ALS lead series suitable for preclinical drug development have been identified each targeting a different aberrant assembly machine involved in ALS.

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even if those funds come to an institution.; Study largely funded by Prosetta, but not own salary.
V.R. Lingappa: A. Employment/Salary (full or part-time):; FTE Prosetta.

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.09/W17

Topic: C.05. Neuromuscular Diseases

Support: Health Research Board

Title: Systemic Angiogenin delivery reverses defects in spinal cord capillary density and delays motor dysfunction in $SOD1^{G93A}$ mice

Authors: *J. H. PREHN[1], M. CRIVELLO[2], S. O'RIORDAN[2], I. WOODS[2]
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Abstract: Loss-of-function mutations in the Angiogenin (*ANG*) gene have been identified in patients with familial and apparently 'sporadic' forms of ALS. Previous work from our group identified Angiogenin as a protective factor for cultured primary motor neurons under stress conditions, and provided *in vivo* proof-of-concept that daily intraperitoneal (i.p.) injections of Angiogenin protein *post* symptom onset increased lifespan and delayed disease progression in $SOD1^{G93A}$ mice. Angiogenin's mechanism of action after systemic administration *in vivo* however remains less well understood. In the present study, we implemented a preclinical *in vivo* study design using sex- and litter-matched $SOD1^{G93A}$ mice to validate our previous *in vivo* report, provide pharmacokinetic data on serum levels and protein distribution after i.p. administration *in vivo*, and to explore Angiogenin *in vivo* acted on cells other than motor neurons. $SOD1^{G93A}$ mice (n=43) and non-transgenic controls (n=30) were sex- and litter-matched according to the Ludolph *et al.* guidelines, and treated with Angiogenin (1 µg, i.p., 3 times/week) or vehicle from symptom onset (90 days). Increased Angiogenin serum levels were detectable 2 and 24 h after i.p. injection in both transgenic and non-transgenic mice. Angiogenin was taken up by Podocalyxin-positive cells, suggesting a vascular mechanism of action. Treatment with Angiogenin increased survival ($p<0.05$) and delayed the onset of motor dysfunction assessed by Rotarad analysis ($p < 0.05$). To determine changes in vascularization and motor neuron degeneration, Angiogenin or vehicle were administered from 90 days until 115 days after which spinal cords were assessed histologically. Stereological measurements of vessel number, density and volume indicated that vehicle-treated $SOD1^{G93A}$ mice showed decreased vascular coverage, and that Angiogenin treatment resulted in improved maintenance of vascular integrity and increased motor neuron survival. Our data suggest that Angiogenin represents a new class of ALS therapeutics that also acts on the spinal cord vasculature to delay disease progression.

Disclosures: **J.H. Prehn:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RCSI. **M. Crivello:** None. **S. O'Riordan:** None. **I. Woods:** None.

Poster

670. Motor Neuron Disease: Therapeutics

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NIEHS (ES009089)

NIGMS (R25GM62454-06)

Calderone award (Mailman School of Public Health at Columbia University)

Title: PK11195, a ligand of the translocator protein 18KDa, improves grip strength, motor performance, and muscle innervation at early but not late disease stages in the amyotrophic lateral sclerosis mutant superoxide dismutase 1 mouse model

Authors: *T. OBIS[1], M. LOTH[1], A. RAMIREZ[4], S. MERWIN[1], B. BLANCO[2], S. GUARIGLIA[1], V. ILIEVSKI[1], S. TAMANINI[4], N. COMFORT[1], Y. NUNEZ[1], M. MUNOZ[1], M. GAMBLE[1], V. JACKSON-LEWIS[3], S. KARIYA[2], S. CORTI[4], T. R. GUILARTE[5], D. B. RE[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is an incurable fatal paralytic disease that affects adults. ALS is characterized by the degeneration of both upper and lower motor neurons (MNs). This study investigated the therapeutic value of the translocator protein 18KDa (TSPO) ligand PK11195 (PK), which we found to be highly protective for MNs and their processes against ALS astrocyte toxicity in both the superoxide dismutase 1 (SOD1) rodent and human co-culture models of ALS that we previously developed (Nagai et al., 2007; Re et al., 2014). Our two goals were: 1) to define the cellular target of PK and its mechanism of neuroprotection in MNs co-cultured with ALS astrocytes; 2) to assess the efficacy of PK in mutant SOD1G93A (mSOD1) mice. *In vitro*, we found that PK acts directly on MNs to prevent their death, not via ALS astrocytes, although TSPO is expressed and up-regulated in both. Immunoelectron microscopy

shows a differential distribution of TSPO among MNs and astrocytes, suggesting cell-specific roles. Knockdown of MN TSPO did not mimic PK protective effect, indicating that is not acting as an antagonist. Also, TSPO is likely part of a neuroprotective pathway as its expression is highest in astrocyte-resistant MNs. For our preclinical study, we determined by high pressure liquid chromatography that PK is quickly eliminated from the CNS after single injection, but is very stable at 37^0C, allowing for its continuous delivery via subcutaneous osmotic mini-pump. 3 groups of mSOD1 mice were formed: vehicle (PEG400), 10 µM, and 100 µM of PK in the pump; both doses lead to significant CNS levels, but only PK10 maintained nM range TSPO-specific levels. mSOD1 mice show a significant deficit at the loaded grid test (grip strength) compared to non-transgenic littermates, as early as 6 weeks (wks) of age, while rotarod score (general motor performance) declines only after 10 wks. Pumps were implanted in 5 wk-old mice and then replaced every 5 wks. Overall, we found that both doses of PK significantly improve grip strength and motor performance, earlier for PK10 (7 vs. 9 wks) but more sustainably for PK100, while both effects lessen with paralysis progression (gone by 16 wks). In agreement, histopathological analyses show a striking dose-dependent protection of neuromuscular junctions (NMJs) in 8-9 wk-old mice. At 14 wks, NMJ preservation has vanished and MN numbers in the lumbar spinal cord are not different among groups. Also, PK does not delay the onset of paralysis (P90-100) and does not extend mouse lifespan. This supports the view that only the combination of therapies targeting neuroprotection and the lessening of glial cell neurotoxicity will hold some promise for clinical efficacy in ALS.

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Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.11/W19

Topic: C.05. Neuromuscular Diseases

Title: Silencing of the mutant huntingtin gene via CRISPR-Cas9 in an *In vitro* model of Huntington's disease

Authors: *N. KOLLI[1,6], M. LU[2,6], P. MAITI[3,7], J. ROSSIGNOL[6,3], G. L. DUNBAR[4,6,5]
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Abstract: Huntington's disease (HD) is a fatal neurodegenerative genetic disease characterized by a loss of neurons in the striatum. It is caused by a mutation in the Huntingtin gene (*HTT*) that codes for the protein huntingtin (HTT). The mutant Huntingtin gene (m*HTT*) contains extra poly-glutamine (CAG) repeats from which the translated mutant huntingtin proteins (mHTT) undergo inappropriate post-translational modifications, conferring a toxic gain of function, in addition to its non-functional property. In order to curb the production of the mHTT, we have constructed two CRISPR (clustered regularly interspaced short palindromic repeat)-Cas9 (CRISPR associate protein) plasmids, among which one nicks the DNA at untranslated region upstream to the open reading frame (uORF), and the other nicks the DNA at exon1-intron boundary. The primary goal of this study was to apply this plasmid into mesenchymal stem cells (MSCs) extracted from the bone-marrow of YAC128 mice, which carries the transgene for HD. Our results suggest that the disruption of uORF through CRISPR-Cas9 influences the translation of mHTT negatively and, to a lesser extent, disrupts the exon1-intron boundary, which affects the translation of the mHTT. These findings also revealed the pattern of the nucleotide addition or deletion at the site of the DNA-nick in this model.
Keywords: Huntington's disease; CAG repeat; mutant huntingtin; gene editing; CRISPR-Cas9 system; pattern of NHEJ; YAC128; Kozak sequence

Disclosures: N. Kolli: None. **M. Lu:** None. **P. Maiti:** None. **J. Rossignol:** None. **G.L. Dunbar:** None.

Poster

670. Motor Neuron Disease: Therapeutics

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Topic: C.05. Neuromuscular Diseases

Support: BioRegioN ERANET Grant 0313610A

CMPB Grant 1356834

Title: Riluzole but not Melatonin ameliorates acute motor neuron degeneration and inhibits disrupted mitochondrial ca2+ signaling in amyotrophic lateral sclerosis

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Abstract: Selective motoneurons (MNs) degeneration in the brain stem, hypoglossal motoneurons (HMNs), and the spinal cord resulting in patients paralysis and eventual death are prominent features of amyotrophic lateral sclerosis (ALS). Previous studies have suggested that mitochondrial respiratory impairment, low Ca^{2+} buffering and homeostasis and excitotoxicity are

the pathological phenotypes found in mice, and cell culture models of familial ALS (fALS) linked with Cu/Zn-superoxide dismutase 1 (SOD1) mutation. In our study, we aimed to understand the impact of riluzole and melatonin on excitotoxicity, neuronal protection and Ca^{2+} signaling in individual HMNs ex-vivo in symptomatic adult ALS mouse brain stem slice preparations and in WT and SOD1-G93A transfected SH-SY5Y neuroblastoma cell line using fluorescence microscopy, calcium imaging with high speed charged coupled device camera, together with immunohistochemistry, cell survival assay and histology. In our experiments, riluzole but not melatonin ameliorates MNs degeneration and moderately inhibit excitotoxicity and cell death in SH-SY5Y^{WT} or SH-SY5Y^{G93A} cell lines induced by complex IV blocker sodium azide.

In brain stem slice preparations, riluzole significantly inhibit HMNs cell death induced by inhibiting the mitochondrial electron transport chain by Na-azide. In the HMNs of brainstem slice prepared from adult (14-15 weeks) WT, and corresponding symptomatic SOD1^{G93A} mice, we measured the effect of riluzole and melatonin on $[Ca^{2+}]i$ using fura-2 AM ratiometric calcium imaging in individual MNs. Riluzole caused a significant decrease in $[Ca^{2+}]i$ transients and reversibly inhibited $[Ca^{2+}]i$ transients in Fura-2 AM loaded HMNs exposed to Na-azide in adult symptomatic SOD1^{G93A} mice. On the contrary, melatonin failed to show similar effects in the HMNs of WT and SOD1^{G93A} mice. Intrinsic NADH fluorescence, an indicator of mitochondrial metabolism and health in MNs, showed enhanced intrinsic NADH fluorescence in HMNs in presence of riluzole when respiratory chain activity was inhibited by Na-azide. Riluzole's inhibition of excitability and Ca^{2+} signaling may be due to its multiple effects on cellular function of mitochondria. Therefore formulating a drug therapy to stabilize mitochondria-related signaling pathways using riluzole might be a valuable approach for cell death protection in ALS. Taken together, the pharmacological profiles of the riluzole and melatonin strengthen the case that riluzole indeed can be used as a therapeutic agent in ALS whereas claims of the efficacy of melatonin alone need further investigation as it fail to show significant neuroprotection efficacy.

Disclosures: M.K. Jaiswal: None.

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

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Program#/Poster#: 670.13/W21

Topic: C.05. Neuromuscular Diseases

Support: VA 1 I01 RX001262A1

Title: Increased frequency of pudendal nerve stimulation improved recovery from a dual nerve and muscle injury

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Abstract: Stress Urinary Incontinence is the involuntary leakage of urine. The primary risk factor in women is childbirth, which injures the pudendal nerve and the external urethral sphincter, creating a dual muscle & nerve injury and pudendal nerve dysfunction up to 5 years after delivery. Electrical stimulation (ES) of injured nerves can accelerate nerve regeneration and functional recovery. Twice weekly stimulation has been shown to decrease functional recovery time after simulated childbirth injury in rats consisting of pudendal nerve crush (PNC) and vaginal distension (VD). We hypothesize that daily electrical stimulation will result in greater improvement in recovery after PNC+VD than less frequent stimulation.
Sprague-Dawley rats either received PNC+VD or sham injury; half of sham injured rats and all PNC+VD rats had wire electrodes implanted. Sham injured rats with electrodes receive sham stimulation (SI + SS). One third of PNC+VD rats received sham stimulation (PNC+VD + SS), an additional 1/3 received electrical stimulation 4 times a week (PNC+VD + 4ES) and the remaining animals received daily stimulation (PNC+VD + DES). Stimulation lasted 1 hour at 20 Hz, 0.1ms, 0.3mA under isoflurane anesthesia; sham stimulation consisted of 1 hour of isoflurane anesthesia. Animals were stimulated for 2 weeks after the injury and survived another 2 weeks when leak point pressure (LPP) with simultaneous external urethral sphincter electromyography (EUS EMG) and pudendal nerve sensory branch potential (PNSBP) were recorded. Data is shown as mean ± sem. An ANOVA followed by a Student-Newman-Keulsposthoctest was used to determine significant differences between groups ($p<0.05$).
LPP was not significantly decreased after PNC+VD + 4ES (39.9 ± 3.0 cm H_20) compared to sham injury no implant (SI +NI; 40.6 ± 3.45 cm H_20) or SI + SS groups (39.9 ± 2.31 cm H_20), although LPP of PNC+VD + SS (19.0 ± 2.43 cm H_20) and PNC+VD + DES (26.5 ± 1.96 cm H_20) rats were significantly decreased. EUS EMG amplitude was significantly decreased after PNC+VD + SS (1.5 ± 2.33μV) and PNC+VD + DES (1.2 ± 0.52μV) compared to SI + NI (13.5 ± 3.79μV) and SI + SS (13.7 ± 3.97μV), but not in PNC+VD + 4ES (5.8 ± 1.92μV). All electrode implanted groups: SI + SS (0.2 ± 0.09 μV), PNC+VD + SS (0.1 ± 0.02 μV), PNC+VD + 4ES (0.2 ± 0.10 μV), and PNC+VD + DES (0.1 ± 0.04 μV) had a significant reduction in PNSBP amplitude compared to IS + NI (0.6 ± 0.06 μV).
While 4 stimulations per week improved LPP and EUS EMG beyond daily stimulation, it did not influence PNSBP recovery. The implanted electrodes likely had a negative effect on the pudendal nerve, since the SI + SS group had a reduction in PNSBP amplitude.

Disclosures: B.M. Balog: None. **D. Lin:** None. **B. Hanzlicek:** None. **M.S. Damaser:** None.

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.14/W22

Topic: C.05. Neuromuscular Diseases

Support: VA I01 RX000228

Title: Brain-derived neurotrophic factor treatment leads to partial recovery after a dual nerve and muscle injury

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Abstract: Stress urinary incontinence (SUI) is a prevalent disorder affecting 30% of women over the age of 40. The primary risk factor for SUI is childbirth which injures both the pudendal nerve and the muscle it innervates: the external urethral sphincter, creating a dual muscle & nerve injury. Upregulation of brain-derived neurotrophic factor (BDNF) is needed for neuroregeneration but can inhibit myogenesis. Treatment with the secretions of mesenchymal stem cells (MSCs), which contain BDNF, accelerates functional recovery in a rat model of SUI consisting of pudendal nerve crush (PNC) and vaginal distension (VD). We hypothesize that the accelerated functional recovery via CCM treatment is caused by the BDNF accelerating the recovery of the pudendal nerve and functional recovery.
Bone marrow-derived MSCs were collected from Sprague-Dawley donor rats and cultures. BDNF knockdown (KD) MSCs were created using an anti-BDNF shRNA lentivirus vector. A scrambled sequence was used as a transfection control (scrambled). Cells were cultured for 24 hours in serum and antibiotic free media before the Media was concentrated 50x to create concentrated conditioned media (CCM) containing the secretions of MSCs. Unmanipulated cells were used to create control CCM. Concentrated control media (CM) was created with media that was not conditioned by cells. Rats underwent a PNC+VD or Sham injury (SI). One hour and 1 week after injury animals received 300µl treatment intraperitoneally. SI rats received CM; PNC+VD rats received CM, CCM, KD CCM or scrambled CCM. Three weeks later, rats underwent leak point pressure (LPP) and pudendal nerve sensory branch potential (PNSBP) recordings. The urethra and pudendal nerve were harvested for histological assessment. An ANOVA followed by a Student-Newman-Keuls posthoc test was used to determine significant

differences between groups ($p<0.05$).
LPP was significantly decreased in PNC+VD + CM (28.3 ± 2.1 cm H_2O) or KD CCM (31.1 ± 2.5 cm H_2O) compared to SI (40.9 ± 3.3 cm H_2O), but not with scrambled (36.0 ± 3.1 cm H_2O) or CCM (51.1 ± 3.1 cm H_2O). PNSBP firing rate showed a significant decrease in CM treatment (399 ± 100 Hz) compared to SI (977 ± 93 Hz). Immunofluorescence showed healthier neuromuscular junction in the sphincter in KD CCM, scrambled CCM, and CCM but not CM compared to SI.
While the immunofluorescence and PNSBP shows regeneration of the pudendal nerve and recovery of its function with any CCM treatment, the LPP results for KD CCM animals would suggest it may take longer to recover continence without BDNF. This study shows while BDNF is important, it is not the only factor needed for the recovery from a dual nerve and muscle injury.

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Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.15/W23

Topic: C.05. Neuromuscular Diseases

Support: IWT

Title: Genome wide genetic screen in *Drosophila* identifies 75 potential modifiers of ALS-FUS toxicity

Authors: J. STEYAERT[1,2], W. SCHEVENEELS[1,2], P. VAN DAMME[3,2,1], W. L. ROBBERECHT[3,2], P. CALLAERTS[4], E. BOGAERT[1,2], *L. M. VAN DEN BOSCH[5,2]
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Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) belong to a group of complex neurodegenerative disorders. Patients with ALS show loss of motor neurons, resulting in progressive muscle weakness, whereas FTD is characterized by the degeneration of the frontal and temporal lobes, resulting in early dementia. Clinical overlap between both diseases is described, suggesting them to be the borders of a disease spectrum. A subgroup within this spectrum, the FUSopathy, is characterized by FUS inclusions in neurons and glial

cells. To gain insight into the pathogenetic mechanism of FUS pathology, we set up an unbiased screen in a drosophila model. In this model, mutant and WT FUS overexpression in the motor neurons results in a pharate adult eclosion defect. We identified 75 candidate genes, able to modify this phenotype. It became apparent that many proteins in this list were present in intracellular RNA granules. Combining this with the fact that FUS inclusions in ALS and FTD patients are positive for stress granule markers, further validation experiments will be performed to investigate the functional importance of these candidate proteins for FUS positive granules.

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Poster

670. Motor Neuron Disease: Therapeutics

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Topic: C.05. Neuromuscular Diseases

Support: SAF-2016-79774-R

CIBERNED

TERCEL

Title: Effects of interleukin-37 in amyotrophic lateral sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that affects upper and lower motor neurons (MNs). MNs loss results in skeletal muscle weakness, spasticity and paralysis, leading to the death of patients by respiratory failure 3 to 5 years after diagnosis. As occurs in several neurological disorders including ALS, inflammation is a pathological hallmark. Several reports have provided evidence that glial cells and leukocytes accelerate the course of the disease in animal models of ALS, suggesting that therapies aimed at targeting inflammation may be a valuable approach for this neurodegenerative disease. IL-37 is the only member of the IL-1 family that exerts broad anti-inflammatory effects over innate and acquired immunity. We have previously demonstrated that IL-37 mediates marked anti-inflammatory actions in the injured central nervous system, and confers protections against secondary tissue damage and functional deficits after spinal cord contusion injury in mice. However, whether IL-37 exerts similar beneficial effects in neurodegenerative conditions is not known yet. In the

present study, we investigated whether IL-37 suppresses inflammation and slows the clinical course of the disease in a mouse model of ALS ($SOD1^{G93A}$ mouse). Since no mouse genomic sequence corresponding to human IL-37 has been found yet, we crossed transgenic mice expressing the human form of IL-37 with $SOD1^{G93A}$ mice to assess the effects of IL-37 in ALS. Our data reveals that transgenic expression of IL-37 slowed ALS disease progression, extended lifespan of $SOD1^{G93A}$ mice, and increased the preservation of spinal cord motoneurons. We also observed that IL-37 attenuated microgliosis and astrogliosis in the lumbar spinal cord of $SOD1^{G93A}$ mice. Since microgliosis and astrogliosis are regulated, in part, by cytokines, we assessed whether IL-37 modulated the protein levels of several cytokines in the sciatic nerve and spinal cord of ALS mice. Luminex experiments revealed that IL-37 attenuated the expression of IL-4 and IL-6 in the sciatic nerve of $SOD1^{G93A}$ mice and reduced the levels of MCP1 in both, sciatic nerve and spinal cord. Interestingly, IL-37 increased in ~4 fold the protein levels of the anti-inflammatory cytokine IL-10 in the spinal cord. This data demonstrates the anti-inflammatory and beneficial actions of IL-37 in a mouse model of ALS. Since previous studies reveal that IL-37 can act extracellularly by forming a complex with the IL-18Rα and IL-1R8, as well as, by translocating to the nucleus, we will dissect out, in future experiments, to what degree the beneficial actions of IL-37 in ALS are mediated via extracellular or intracellular function.

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Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: C.05. Neuromuscular Diseases

Support: BMBF (GO-Bio)

Title: *In vivo* safety and efficacy evaluation of a novel 3rd generation antisense oligonucleotide against TGFßRII to treat amyotrophic lateralsclerosis

Authors: *S. PETERS[1], E. ZITZELSPERGER[1], S. KUESPERT[1], R. HEYDN[1], L. J. AIGNER[2], S. KORTE[3], T.-H. BRUUN[1], U. BOGDAHN[1]
[1]Dept. for Neurol., Univ. Hosp., Regensburg, Germany; [2]Paracelsus Med. Univ., Salzburg, Austria; [3]Covance Preclinical Service GmbH, Münster, Germany

Abstract: Amyotrophic Lateralsclerosis (ALS) is a fatal neurodegenerative disease in adults with a progressive loss of upper and lower motorneurons. ALS patients exhibit an enhanced TGFß system activity critically mediating the imbalance of neurodegeneration and neuroregeneration. Neurodegeneration is accompanied by a profound pro-inflammatory and neurotoxic immune profile, an inhibited/arrested adult neurogenic niche activity, and an

increased pro-fibrotic status. A novel 3rd generation antisense oligonucleotide (ASO) targeting the TGFßRII, significantly reaches target and modulates all three pathophysiological aspects of neurodegeneration in human neuronal progenitor cells (ReNcell CX). We first investigated ASO tolerability by using a dose escalation paradigm with increasing dose levels every single week for 4 weeks. One male and female Cynomolgus monkey received an intrathecal ASO injection and physical/neurological parameters were investigated directly and following 4h after administration. For clinical chemistry, bioanalytics, biomarker determination, and target regulation, blood and CSF samples were taken before each dosing and tissue samples (liver, kidney, spinal cord, brain) were collected at the end of the study. In a second study ASO pharmacokinetics was evaluated by bioanalytical determination of ASO tissue concentrations following 2 or 4 wks post intrathecal drug administration of two different ASO doses. CSF was taken before necropsy to determine ASO half-life. Further, CNS tissue samples (spinal cord, brain) were collected to evaluate tissue distribution. Finally, in a third paradigm the ASO was injected repeatedly over a 13-week approach at two different doses to simulate a long-time administration period and to investigate possible ASO saturation levels. For analysis, blood, CSF and tissue samples were taken as described for the tolerability study. Target regulation as well as TGFß system activity with the expression levels of the ligands and the most important downstream target molecules was determined within the spinal cord, motor cortex, dentate gyrus, and the subventricular zone. Consequently, effects of an altered TGFß system activity on the adult neurogenic niche was investigated by measuring neuronal stem cell and neurogenesis markers. All parameters of interest were determined via qRT-PCR, Western Blot analysis, and immunofluorescence staining. Taken together, the results of the current study indicate that the novel 3rd generation ASO is a well tolerated, stable and efficient molecule to alter TGFß system and adult neurogenic niche activity. Therefore, it might represent a potential candidate to treat ALS.

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Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.18/W26

Topic: C.05. Neuromuscular Diseases

Title: Widespread spinal cord transduction with a modified AAV vector: Implications for spinal cord diseases

Authors: J. NAIDOO[1], *L. M. STANEK[2], P. HADACZEK[1], L. SAMARANCH[1], C. O'RIORDAN[2], J. BRINGAS[1], C. SNIECKUS[1], J. SULLIVAN[2], S. NASS[2], M. MATTINGY[2], D. WOODCOCK[2], K. S. BANKIEWICZ[1], L. SHIHABUDDIN[2]
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Abstract: Background: A key limiting factor for the clinical application of gene therapy in spinal cord disorders is the low levels of transduction that current vectors can achieve in the motor neurons (MN) of spinal cord. We have addressed this issue with a modified adeno-associated viral vector capsid (AAV*). **Objective:** The goal of this study was to evaluate the efficiency of MN transduction of AAV*-GFP in non-human primate (NHP) after either lateral ventricle or thalamus delivery. **Methods:** Six adult male NHP (*Macaca mulatta*), negative for neutralizing antibodies against the AAV capsid, were randomized assigned to two treatment groups. Group I (n=3) received a single dose of AAV*-CBA-eGFP into lateral ventricle (1.5 mL/hemisphere) and animals from group II (n=3) received an injection into thalamus (130 - 280µL/hemisphere). All injections were performed under magnetic resonance imaging (MRI) guidance. Three weeks later, spinal cords were harvested, and 15 µm sections were analysed by immunohistochemistry against GFP and NeuN. Percentage of MN transduction was determined on consecutive sections from cervical, thoracic, lumbar and sacral regions. **Results:** Robust GFP expression was observed in both cell bodies and fibres in all regions of the spinal cord after lateral ventricle injection. 92.8% of MN were transduced in the cervical region, 83.6% in thoracic, 85.1% in lumbar and 92.6% in sacral region. On the other hand, animals with a thalamic infusion showed levels of transduction of 64.8% in cervical, 33.5% in thoracic, 38.3% in lumbar and 33.0% in sacral regions. Further analysis for immune reaction reveled no perivascular infiltration, microglia hyper-reactive or astrocytic activation in any of the treated groups. **Conclusion:** Lateral ventricle injection of a modified AAV vector can globally transduce MN of the spinal cord with no significant immune response.

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Poster

670. Motor Neuron Disease: Therapeutics

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Topic: C.05. Neuromuscular Diseases

Support: This study was funded by Genervon Biopharmaceuticals, LLC

Title: GM604 as a novel therapeutic strategy for treatment of ALS and other neurodegenerative diseases: Pre-clinical and bioinformatic data and findings from a phase 2A randomized placebo-controlled clinical trial

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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that lacks effective treatment options. As a novel treatment strategy, Genervon Biopharmaceuticals has discovered and developed GM604 (GM6), a 6-amino acid peptide drug modeled upon an endogenous embryonic protein isolated from the developing nervous system (human motoneuronotrophic factor, MNTF). We have hypothesized that GM6 has multi-target effects replicating the MNTF activity spectrum, leading to improved survival of neurons in neurodegenerative patients. Through *in vivo* pre-clinical studies, we have shown that GM6 prevents functional decline and promotes neuron lesion recovery in rodent models of neurodegenerative disease. These models have included the SOD1-G93A transgenic model (ALS), mice treated with 6-hydroxydopamine or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (Parkinson's disease, PD), and mice injected with myelin proteolipid protein (Multiple sclerosis, MS). *In vitro* assays using rat cortical neurons additionally demonstrated that GM6 protected against toxic factors in CSF isolated from patients diagnosed with these diseases. Using DNA microarrays, we identified 1259 genes altered at least 2-fold in SH-5YSY cells, including 89, 48, 46 and 9 genes associated with ALS, AD, PD and MS, respectively. Functional enrichment analyses of these GM6-sensitive genes suggested cellular changes related to repression of the intrinsic apoptotic pathway and stimulation of mitotic/proliferation pathways. To demonstrate the clinical significance of these findings, we recently reported results from a multi-site phase 2A randomized, double-blind, placebo-controlled pilot trial of GM6 for treatment of ALS. Our phase 2A findings demonstrate clinical safety of GM6 and observed favorable shifts in ALS biomarkers and improved functional measures. In this study, GM6 decreased plasma levels of key ALS biomarkers (TDP-43, $P = 0.008$; Tau, $P = 0.037$; SOD1, $P = 0.009$). Compared to a historical control cohort in definite ALS patients, GM6 slowed functional decline based upon the

ALS Functional Rating Scale (P = 0.005), and we observed site-specific improvement in forced vital capacity (P = 0.027). These findings support the hypothesis that GM6 triggers developmental-stage cascades to ultimately encourage neuron survival to attenuate progression of neurodegenerative diseases. We are now conducting a new generation of studies to better delineate mechanisms by which GM6 may promote neuron survival (e.g., using high-throughput complementary DNA sequencing, RNA-seq). We have designed a phase 3 ALS randomized placebo-controlled trial planning to start in 2017.

Disclosures: **M.S. Kindy:** None. **K. Bojanowski:** None. **P. Lupinacci:** None. **T.K. Shum:** None. **D. Ko:** A. Employment/Salary (full or part-time):; Dorothy Ko is an executive of Genervon Biopharmaceuticals, LLC, the sponsor of the trial. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dorothy Ko has ownership interest in Genervon Biopharmaceuticals, LLC.

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.20/W28

Topic: C.05. Neuromuscular Diseases

Support: AurimMed Pharma, Inc.

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Nemours Foundation

Title: Identification of novel CNS-active inducers of SMN2 expression

Authors: ***M. E. BUTCHBACH**[1,2,3], R. W. KIRK[1], A. W. HARRIS[1], K. M. HINKLE[2], A. J. CONNELL[1], A. PESYAN[4]
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Abstract: Spinal muscular atrophy (SMA), a leading genetic cause of infant death worldwide, is an autosomal recessive motor neuron disease caused by the loss of *SMN1* but retention of *SMN2*. The number of copies of *SMN2* inversely correlates with disease severity in SMA patients making *SMN2* a target for therapeutics development. AurimMed Pharma, Inc. has developed a focused library of potent CNS active compounds. In this study, we screened this library for modulators of *SMN2* expression using reporter cell lines as well as fibroblasts derived from SMA

patients. The compound library was screened using NSC34 motor neuron-like cell lines expressing either a reporter gene under the control of the 3.4 kb *SMN2* promoter or a mini-gene construct containing exons 6 through 8 of *SMN2* as well as their intervening introns. The effects of hit compounds on *SMN2* expression were measured in type II SMA fibroblasts (GM03813) by quantitative real-time PCR, immunoblot and immunofluorescence. Of the 64 compounds in this library, 26 showed enhanced *SMN2* promoter activity relative to vehicle (DMSO)-treated cells and 5 showed increased inclusion of exon 7. Some of these hits were validated in GM03813 type II SMA fibroblasts. 5 compounds—AMP-X-0079, AMP-X-0080, AMP-X-0026, AMP-X-0009 and AMP-X-0024—increased *SMN2* mRNA and protein levels in these cells. We have identified new compounds that increase *SMN2* expression in NSC34 cells and in SMA fibroblasts. Future work will determine the mechanisms by which these compounds are increasing *SMN2* expression. Furthermore, these compounds will be moved forward into preclinical studies using mouse models of SMA.

Disclosures: **M.E. Butchbach:** 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.; AurimMed Pharma, Inc.. F. Consulting Fees (e.g., advisory boards); AurimMed Pharma, Inc.. **R.W. Kirk:** None. **A.W. Harris:** None. **K.M. Hinkle:** None. **A.J. Connell:** None. **A. Pesyan:** A. Employment/Salary (full or part-time):; AurimMed Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AurimMed Pharma, Inc..

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.21/W29

Topic: C.05. Neuromuscular Diseases

Support: ALS Association

Title: Promotion of the M2 microglial state and enhanced neuronal trophic support extend survival in the murine model of ALS

Authors: *A. M. SNYDER[1], E. B. NEELY[1], O. MROWCZYNSKI[1], R. PAYNE[1], A. GERONIMO[3], Z. SIMMONS[2], J. R. CONNOR[1]
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Abstract: Amyotrophic Lateral Sclerosis is a multi-faceted disease with microglial activity impacting the environment for motor neuron viability. Biomarker analyses indicate that ALS

patients with a longer survival time have increased levels of trophic factors that support M2 microglia polarity, suggesting that this may be a point for therapeutic intervention. Our objective is to determine if providing metabolic support *in vivo* to neurons and promoting the M2 microglial phenotype extends survival in the well-characterized $SOD1^{G93A}$ murine model of ALS. At 80 days of age, ozmotic mini-pumps were loaded with our formulation of an artificial CSF (SCSF) solution with interleukin 9 (IL-9), granulocyte colony stimulating factor (G-CSF), chemokine (C-C motif) ligand 2 (MCP-1), and macrophage inflammatory protein-1-β (MIP-1β). A group of animals with received PBS infusion as an infusion control. Disease onset was assessed by performance on the rotarod apparatus, and endpoint was determined by the inability of the animal to right itself after 30 seconds. In a sub-set of animals, behavioral analyses extended beyond onset to determine the fall rate as disease progressed towards endpoint. Our results suggest that infusion with SCSF with factors that promote M2 microglial polarity extend survival rates in the murine model. There was a 3 day extension in survival as compared to the No surgery group and a 5 day extension as compared to the PBS-infused group, suggesting that infusion of a buffer solution that clears the CSF, such as PBS, is inadequate to positively impact disease progression. The rate of falls after disease onset was more severe in the PBS group, suggesting that this data may be informative in correlating murine behavioral data to for quality of life in the human population.

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Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

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Program#/Poster#: 670.22/W30

Topic: C.05. Neuromuscular Diseases

Support: SAF-2016-79774-R

Title: Involvement of the LPA-LPA_2 axis in the physiopathology of ALS

Authors: *M. PUIGDOMENECH POCH, A. MARTINEZ-MURIANA, R. LÓPEZ-VALES
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Abstract: Lysophosphatidic acid (LPA) is a pleiotropic extracellular lipid mediator with many physiological functions that signals through 6 known G protein-coupled receptors (LPA_{1-6}). LPA_{1-3} share high homology in amino acid sequence and belong to the endothelial differentiation gene (edg) family LPA receptors, whereas LPA_{4-6} are genetically more distant and belong to the non-edg family LPA receptors. LPA mediates a wide range of LPA effects in the central nervous system, including neural progenitor cell physiology, glial activation, neuronal cell death, and

axonal retraction. We have previously shown that microglial cells become cytotoxic upon LPA-LPA_1 activation and lead to myelin loss after spinal cord injury. We have also unpublished data indicating that activation of microglia LPA_2 also leads to demyelination, as well as, to neuronal loss, especially motor neurons, after spinal cord injury. Similar detrimental actions of LPA have been also shown after brain injury by using an LPA antibody. Since microgliosis is a common hallmark of most neurological conditions, we hypothesized that LPA could be involved in the pathophysiology of neurodegenerative diseases, such amyotrophic lateral sclerosis (ALS). This is a fatal neurodegenerative disease characterized by the loss of upper and lower motor neurons. The underlying mechanisms leading to the degeneration of motor neurons in ALS are diverse and not fully known, however, there is evidence supporting the detrimental action of inflammation in the course of this disease. However, whether LPA is involved in the physiopathology of ALS has not been studied yet. Since our unpublished data shows that LPA-LPA_2 axis is involved in motor neuron death after spinal cord injury, we assessed whether activation of LPA_2 contributes to ALS. With this purpose, we crossed LPA_2 null with $SOD1^{G93A}$ mice and characterized the course of the disease by means of functional and electrophysiological tests. Our results revealed that the decline of the amplitude of the compound muscle action potential of the tibialis anterior muscle was slower in ALS mice lacking LPA_2 as compared to WT littermates, suggesting that the neuro-muscular integrity was better preserved in the absence of LPA_2 activity. Similarly, rotarod testing showed that the lack of LPA_2 also resulted in delayed onset and slowed progression of the disease. To our knowledge, these data suggests for the first time the detrimental actions of the LPA-LPA_2 axis in the physiopathology of ALS.

Disclosures: **M. Puigdomenech Poch:** None. **A. Martinez-Muriana:** None. **R. López-Vales:** None.

Poster

670. Motor Neuron Disease: Therapeutics

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 670.23/W31

Topic: C.05. Neuromuscular Diseases

Support: 82108315

Title: Moving towards the clinic: Intrathecal aav9-sod1-shrna administration for amyotrophic lateral sclerosis

Authors: ***S. B. LIKHITE**, S. CORCORAN, C. BEST, L. BRAUN, K. MEYER, B. K. KASPAR
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is an adult-onset neurodegenerative disease, characterized by loss of motor neurons, progressive paralysis and death. Dominant mutations in the superoxide dismutase 1 (SOD1) gene are among the most frequent causes of inherited ALS. In our previous studies, we utilized Adeno-Associated Virus Serotype 9 (AAV9) carrying a GFP reporter to deliver a short hairpin RNA (shRNA) downregulating SOD1. This vector significantly improved disease outcome in mouse models. The treatment was safe and well-tolerated, but the presence of a foreign transgene and regulatory elements excluded a direct application of this vector in clinical trials. Hence, the main objective of the current study was to design and test the efficacy of an AAV9-SOD1-shRNA vector devoid of any foreign transgenes, enabling its direct use in clinical trials. We determined the *in vitro* efficiency of SOD1 downregulation and *in vivo* efficacy to delay the disease onset and progression with the modified AAV9 vector carrying SOD1 shRNA expression cassette and a non-coding stuffer sequence instead of GFP. In mice, we tested 2 different delivery routes for vector administration: intravenous (IV) and intracerebroventricular (ICV). Male and female SOD1G93A mice, overexpressing human mutant SOD1, were administered with modified AAV9-SOD1-shRNA vector via IV or ICV at postnatal day 1 and monitored throughout their lifespan. Both treatments resulted in significant improvement in rotarod performance and hindlimb grip strength. Moreover, removal of the GFP cassette markedly improved the therapeutic effect of the vector by significantly extending the median survival of ALS mice by 70 days which is almost twice the effect achieved with pervious construct. Importantly, similar therapeutic effect was achieved by ICV delivery of the vector at a 10-fold lower dose as compared to IV. To translate this approach to clinic, we also administered AAV9-SOD1-shRNA vector in adult (10 year old) non-human primates (Rhesus monkeys). A single intra-lumbar infusion of the vector resulted in significant SOD1 reduction throughout the monkey brain and spinal cord, thus corroborating our dosing rationale and route of delivery. In summary, we have successfully designed and tested the modified AAV9-SOD1-shRNA vector that would meet FDA requirements. We report one of the longest survival extensions achieved in the most severe ALS mouse model, using just a single CSF administration of AAV9-SOD1-shRNA. Finally, successful translation of this therapy in non-human primates paves the way for future clinical trials for ALS patients.

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Poster

670. Motor Neuron Disease: Therapeutics

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Support: The Audrey E. Streedain Regenerative Medicine Initiative Award

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The Muscular Dystrophy Association Development Grant

The Student Opportunities for Academic Research, University of Southern California

Title: Excising the ALS/FTD-associated C9ORF72 repeat expansion with CRISPR-Cas9 *In vivo*

Authors: C. P. SEAH[1], *K. A. STAATS[2], N. KOUTSODENDRIS[1], M. CHATEAU[3], D. KIM[1], M. J. COWAN[1], Y. SHI[1], P. CANNON[3], J. K. ICHIDA[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are devastating and incurable neurodegenerative diseases characterized by a progressive loss of neurons. An intronic GGGGCC repeat expansion in the gene C9ORF72 is the most common cause of both ALS and FTD, accounting for over 10% of each disease. The precise disease mechanisms by which this repeat expansion causes disease is not fully understood, yet both gain- and loss- of function of the mutant allele are expected to contribute to disease. Here, we aim to circumvent addressing disease mechanisms by targeting the repeat expansion directly. We employ the gene-editing strategy of CRISPR-Cas9 and delivery by AAV9. By intrathecal injection in mouse neonates we obtain a high transduction efficiency with AAV9-GFP in the spinal cords, predominantly transducing large motor neurons, as well as transduce neurons in different areas of the brain, including cerebellum and hippocampus. For optimal AAV9 packaging, we use a split Cas9 enzyme. Our designed CRISPR-Cas9 guide RNAs are compatible with this enzyme and cut close to the repeat expansion without disruption of the C9ORF72 coding sequence. These guide RNAs are tested in human HEK293T cells for excision efficiency. We utilize commercially available C9ORF72-BAC transgenic mice and assess cellular readouts, such as dipeptide repeat proteins and RNA foci, to confirm excision in transduced cells. This research is the first step in ALS and FTD towards assessing the potential of CRISPR-Cas9 gene-therapy in vivo.

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Poster

670. Motor Neuron Disease: Therapeutics

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Topic: C.05. Neuromuscular Diseases

Support: Adelson Medical Research Foundation

Maryland Stem Cell Research Fund

Title: Searching for new targets to sustain neuromuscular function

Authors: *J. T. EHMSEN[1], R. KAWAGUCHI[2], R. MI[1], D. NACHUN[2], G. COPPOLA[2], A. HÖKE[1]
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Abstract: Skeletal muscle is a highly adaptive tissue capable of changes in size, contractility, and metabolism according to functional demands. Atrophy is a decline in mass and strength caused by pathologic loss of myofibrillar proteins, and is associated with numerous conditions including disuse, immobilization, malignancy, aging (sarcopenia), and denervation caused by injury or motor neuron diseases such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA).
Regardless of the underlying condition, several key signaling pathways have been identified as important mediators of atrophy, including NF-KB and MAPK cascades that lead to induction of key E3 ubiquitin ligases and effectors of proteasomal degradation. Genetic disruption of NF-KB signaling in mouse models is partially protective against muscle atrophy induced by denervation and other physiologic models of atrophy, pointing to its centrality in mediating atrophy. However, denervation-induced triggers and regulators of these cascades within skeletal muscle remain unclear.
In addition to the functional limitations of muscle weakness caused by chronic denervation, chronically denervated muscle shows severely diminished capacity for functional re-innervation. The molecular changes that underlie this resistance to re-innervation are also unclarified.
To begin to add detail to these important features of the atrophic process, we used RNA-Seq to characterize transcriptional changes occurring in mouse gastrocnemius following tibial nerve transection. We performed a longitudinal analysis capturing transcriptional changes occurring acutely after denervation (1 day post-denervation), early changes during the window of most rapid atrophy (3, 7, and 14 days post-denervation), and changes associated with chronic denervation (30 and 90 days post-denervation).
Our data suggest innate immune system signaling and immunoreceptor-like signaling as potential mediators and/or modifiers of denervation atrophy. Inflammatory signatures are still apparent in chronically denervated and severely atrophied muscle, along with gene expression changes suggestive of increased integrin-mediated focal adhesion and altered chromatin structure. We anticipate that further clarifying the origin and consequences of these transcriptional changes will afford new opportunities to modify the course of atrophic disease.

Disclosures: **J.T. Ehmsen:** None. **R. Kawaguchi:** None. **R. Mi:** None. **D. Nachun:** None. **G. Coppola:** None. **A. Höke:** None.

Poster

670. Motor Neuron Disease: Therapeutics

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Topic: C.05. Neuromuscular Diseases

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MDA 351564

NIH Grant U54 OD020351

NIH Grant RO1 NS054154

Title: A personalized gene therapy approach for charcot-marie-tooth disease type 2d

Authors: *K. H. MORELLI[1], K. L. SEBURN[1], N. PYNE[2], A. FOWLER[2], S. Q. HARPER[2], R. W. BURGESS[1]
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Abstract: Charcot-Marie-Tooth Disease (CMT) is a heterogeneous group of inherited peripheral neuropathies affecting 1:2500 individuals worldwide. To date, fifteen different mutations in *GARS (*glycyl-tRNA synthetase*)* have been identified in patients with autosomal dominant CMT Type 2D (CMT2D). Although the mechanisms through which mutant forms of GARS cause axon degeneration remain controversial, preliminary data from CMT2D patients and mouse models of the disease (*Gars*$^{C201R/+}$ and *Gars*$^{P278KY/+}$) suggest that the expression of mutant GARS may cause toxic gain-of-function effects in peripheral nerves. As such, the selective silencing of mutant *GARS* expression should benefit patients with this disorder. In response, we have developed a gene therapy strategy that reduces the expression of mutant *Gars* transcripts through allele-specific RNAi. To test the proof-of-principle of this approach, we developed self-complementary adeno-associated viral vectors (scAAV9) expressing therapeutic microRNAs engineered to specifically silence the mutant mouse *Gars* allele P278KY (referred to as mi.P278KY). Untreated *Gars*$^{P278KY/+}$ mice show a CMT2D-like neuropathy, including motor dysfunction and axon atrophy. We found that scAAV9-mi.P278KY delivered at birth (pre-disease onset) largely prevented these CMT2D-like phenotypes. We are now testing the ability of scAAV9-mi.P278KY delivered after disease onset to arrest or reverse the CMT2D-like neuropathy. To this end, we have shown that scAAV9-mi.P278KY treatment of adult *Gars*$^{P278KY/+}$ mice increases body weight and improves grip strength. We are now evaluating the ability of our gene therapy to rescue axon and muscle degeneration in adult *Gars*$^{P278KY/+}$ mice. In future, we will test efficacy of patient-specific vectors in “humanized” mouse models carrying

CMT2D-patient-associated mutations in the mouse *Gars* gene. Success with this allele-specific approach would provide a promising avenue for treatment of CMT2D and other dominantly inherited neuromuscular diseases.

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Poster

670. Motor Neuron Disease: Therapeutics

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Topic: E.10. Motor Neurons and Muscle

Support: MoST105 2321-B-001-018

Title: The role of D_2 Dopamine receptor in modulating the protective effect of A_{2A} Adenosine receptor in Amyotrophic lateral sclerosis

Authors: *J. LAI[1,2], Y. CHERN[2], Y.-J. LIU[2], H.-L. LAI[2], Y. CHERN[1]
[1]life sciences, Natl. Def. Med. Ctr., Taipei, Taiwan; [2]Academia Sinica/ Inst. of Biomed. Sci., Taipei, Taiwan

Abstract: $A_{2A}R$ is a seven transmembrane protein and couple to Gαs protein that activates cAMP -dependent and -independent pathways upon the stimulation. Dopamine D_2 receptor (D_2R) is also a seven transmembrane protein but couple to Gαi protein that inhibits cAMP dependent signaling and regulates cAMP- independent pathways. It was demonstrated that $A_{2A}R$ forms dimmer and interacts with D_2R in the human and mouse striatum region and several cells lines, such as SHSY5Y and CHO cells. $A_{2A}R$-D_2R complex formation would affect to $A_{2A}R$ or D_2R functions. TAR DNA-binding protein (TDP-43) was detected in the nuclear and regulates transcription and RNA splicing, in normal physiology. In pathological, TDP-43 was found that located in the cytoplasm in several neurodegeneration diseases, such as amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). So far, there is no effective treatment to prevent TDP-43 mislocalization. In our published data indicated that a novel agonist (T1-11 analog) of adenosine $_{2A}$ receptor ($A_{2A}R$) prevented reactive oxygen species (ROS) induced TDP-43 redistribution in a mouse motor neuron cell line (NSC34) and played a neuroprotective role in a TDP-43 transgenic mice. In the following study showed that $A_{2A}R$-D_2R co-expressed on motor neurons of ALS patient's spinal cord tissues and NSC34. $A_{2A}R$-D_2R complex did not modified T1-11binding affinity but diminished downstream signaling cAMP. Activation of D_2R modulated the beneficial effect of $A_{2A}R$, including ROS-induced AMPK-overactivation and TDP-43 distribution in NSC34. Taking together, our study demonstrated that co-activation of $A_{2A}R$-D_2R interrupted the neuroprotection of the $A_{2A}R$ in ALS.

Disclosures: **J. Lai:** None. **Y. Chern:** None. **Y. Liu:** None. **H. Lai:** None. **Y. Chern:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

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Program#/Poster#: 671.01/W36

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Grants (2017R1A2B4004289 and 2012M3A9C6049935)

the DGIST Convergence Science Center Program (17-BD-04) of the Ministry of Science, ICT and Future Planning of Korea

Title: Parkin regulates mitophagic cell death in adult hippocampal neural stem cells following insulin withdrawal

Authors: *H. PARK, K. CHUNG, H.-K. AN, S. JUNG, S.-W. YU
DGIST, Daegu, Korea, Republic of

Abstract: Insulin is a key factor in the hippocampal function, and proliferation of hippocampal neural stem (HCN) cells is dependent on insulin signaling. We have previously demonstrated that adult rat HCN cells undergo autophagic cell death (ACD) following insulin withdrawal despite their intact apoptotic capability. Here, we show that insulin-deprived HCN cells undergo ACD through Parkin-dependent mitophagy. Mitophagy is one of the selective forms of autophagy to maintain healthy mitochondria by degradation of defective or damaged mitochondria in various stress condition. However, excessive mitophagy may also lead to mitophagic cell death. Insulin withdrawal increased the amount of depolarized mitochondria and induced LC3-II translocation from the cytosol to depolarized mitochondria in HCN cells. Interestingly, insulin withdrawal up-regulated both mRNA and protein levels of Parkin in c-Jun-dependent manner. CRISPR/Cas9-mediated knockout of the Parkin gene reduced mitophagy level and ACD. Taken together, these results indicated that Parkin is required for the induction of mitophagic cell death in HCN cells following insulin withdrawal.

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Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.02/X1

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Changes in antioxidant protein expressions in isolated mitochondria of AD transgenic mice brains

Authors: *N. YOSHIDA[1], Y. KATOU[1], A. HIRANO[1], K. NAKAMURA[1], T. MAEHARA[1], H. TAKATSU[2], K. FUKUI[1]
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Abstract: Reactive oxygen species (ROS) attack several living organs and induce cell death. We revealed that treatment with a low concentration of hydrogen peroxide in cultured cells induced neurite degeneration prior to the cell death. At the regions of degeneration, we found mitochondrial accumulation and mitochondrial-dependent super oxide production. From these results, we think that ROS-derived mitochondrial dysfunction is one reason of the neurite degeneration. However, the detailed mechanism of it has not been elucidated. On the other hand, several kinds of evidence have been demonstrated the relationship between ROS-dependent mitochondrial dysfunction and cell death in neurodegenerative disorders. Furthermore, it is well known that mitochondrial disruption is occuerred in Alzheimer's disease (AD) brain. So, here we compared to the antioxidative protein expressions in isolated mitochondria in mice brains, and used as a sample in this study. Nicotinamide adenine dinucleotide quinone oxideredactase 1 (NQO1) expressions were significantly increased in aged AD mice compared to the age-matched control. Conversely, nicotinamide mononucleotide adenylyltransferase 3 (NMNAT-3) and superoxide dismutase 2 (SOD2) expressions in aged AD mice were significantly decreased compared to the age-matched control. NQO1, 3-nitrotyrosine (3-NT) expressions of control group were significantly increased in normal aged mice. Expressions of nNOS were unchanged of all groups. On the other hand, phosphorylated nNOS expression significantly increased in normal aged-group. These results indicate that changes in antioxidative protein expressions may be involved in neurite degeneration and progression of AD.

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Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant EY026662

Title: Optic nerve metabolic vulnerability in DBA/2J model of glaucoma and potential intervention by ketogenic diet

Authors: *M. HARUN-OR-RASHID, D. M. INMAN
Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH

Abstract: Recent evidence supports energy disruption is an early indication of pathology in a wide range of neurodegenerative disease. Reduced ATP production and compound action potentials have been observed in glaucomatous optic nerve (ON), suggesting metabolic dysfunction. These experiments investigated the source of ON metabolic vulnerability and tested whether ketogenic diet can intervene in that vulnerability. We examined energy storage, energy exchange and metabolic control in the ON. DBA/2J (D2) mice that develop glaucoma-related optic neuropathy and age-matched DBA/2J$^{wt\text{-}gpnmb}$ (D2G) control eyes were injected with cholera toxin B (CTB) to assess axon transport status. Mice were grouped by age (3, 6, and 10m); biochemical assays were performed with ON; protein levels were analyzed by WES (Simple western) and immunostaining was performed on ON sections and flat-mount retinas. For the intervention study, 9m old D2 mice were fed with ketogenic and control diets for 8 weeks and analyzed as above. Biochemical analyses showed decreased glycogen, l-lactate, NAD^+ levels and creatine kinase activity in 10m D2 ON compared to 10m D2G, indicating insufficient energy storage and availability in D2 ON. MCT1 and MCT4 transport energy metabolites from glial cells and MCT2 takes up those metabolites into axons. GLUT1 is a glucose transporter specific to glial cells. Significant decreases in MCT1, MCT2, MCT4 and GLUT1 protein levels were observed in 10m D2, which indicate energy transport deficit in ON. We observed robust AMPK activation (phosphorylated-AMPK) in 6m and 10m D2 compared to D2G age groups, indicating high energy demand in the ON. The PGC-1α levels were significantly decreased in 10m D2 compared to 10m D2G, suggesting impaired mitochondrial biogenesis in ON. Feeding of the ketogenic diet enhanced the energy storage in ON by increasing l-lactate, NAD^+ levels and creatine kinase activity. The ketogenic diet significantly improved the energy transport in ON by increasing MCT1 and MCT2 levels, and normalized energy demand as shown by significantly decreased AMPK activation. PGC-1α levels were also significantly increased in the ON of ketogenic mice, suggesting increased mitochondrial biogenesis. CTB transport and RGC numbers were significantly increased in ketogenic mice, demonstrating that the ketogenic diet

prevents axonopathy and retinal ganglion cell loss in glaucoma. Thus, these data conclude that the ON metabolic vulnerability that occurs in glaucoma can be alleviated by the ketogenic diet.

Disclosures: M. Harun-Or-Rashid: None. **D.M. Inman:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.04/X3

Topic: B.08. Synaptic Plasticity

Support: NIH AG000315-16

NIH AG000317-16

Title: Mitochondria-mediated structural and functional adaptations of neuronal circuits to intermittent bioenergetic challenges

Authors: *M. P. MATTSON, A. CHENG, Y. LIU, K. MAROSI, N. GHENA, R. WAN
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Abstract: Evolution favors individuals whose brains and bodies function optimally when in a food deprived/fasted state (imagine a cougar that has not eaten for a week chasing a rabbit, or our human ancestors hunting with bows and arrows). We have been interrogating the cellular and molecular responses of neuronal circuits in the brain to intermittent fasting (IF) and running, and have elucidated structural and functional adaptations involving reciprocal interactions between neurotrophic factor and neurotransmitter signaling pathways, and mitochondrial biogenic and stress adaptations. The ketone 3-hydroxybutyrate, which is generated from fatty acids during fasting and extended exercise, up-regulates BDNF expression in neurons and, in turn, BDNF induces mitochondrial biogenesis via CREB- and PGC-1alpha pathways. Moreover, mitochondrial biogenesis is necessary for BDNF-induced synaptogenesis, suggesting pivotal roles for mitochondria in exercise- and IF-induced synaptic plasticity. IF and running induce the expression of the mitochondrial protein deacetylase SIRT3, and this enzyme protects neurons against metabolic and excitatory stress. SIRT3-mediated neuronal network adaptations to IF involve upregulation of GABAergic tone which constrains neuronal network activity in the hippocampus and amygdala, and is associated with reduced levels of anxiety and sustained cognitive performance. Interestingly, similar to the sleep quality-enhancing effects of regular exercise in humans, we find that mice adapted to IF exhibit a doubling of the time they spend in slow wave sleep, despite a moderate reduction in overall sleep time. Additional implications for human performance come from our recent data demonstrating that endurance is enhanced in mice when they are maintained on IF during treadmill training (see Moehl K et al., poster).

Finally, our findings suggest that bolstering of mitochondrial stress resistance may be an important mechanism by which IF and running increase resistance of neurons to dysfunction and degeneration in neurological disorders ranging from epilepsy and stroke, to Alzheimer's, Parkinson's and Huntington's diseases (see Ghena N et al. poster). Supported by the Intramural Research Program of the National Institute on Aging.

Disclosures: M.P. Mattson: None. **A. Cheng:** None. **Y. Liu:** None. **K. Marosi:** None. **N. Ghena:** None. **R. Wan:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.05/X4

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Calcium ionophore induces neurite degeneration in neuroblastoma cells via mitochondrial membrane oxidations

Authors: *K. FUKUI, S. NAKAMURA
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Abstract: Treatment with a low concentration of hydrogen peroxide induced neurite and axonal degeneration prior to the cell death. We also observed cell membrane oxidations, microtubules alterations and inactivation of autophagy. If cell membranes are oxidized by ROS, a large parts of receptors and ion channels may be also damaged. Here, we show the elucidation of the relationship between calcium influx and neurite degeneration in cultured neurons. Before start of study, we optimized calcium ionophore concentration. Treatment with an ionomycin induced neuronal cell death in a concentration- and a time-dependent manner. Treatment with a low concentration of ionomycin induced neurite degeneration, such as induction of beading and shrinkage formation. Co-treatment with Fluo-4AM, we recorded calcium influx after ionomycin treatment using a time-lapse live imaging system. The relative intensities of Fluo-4AM significantly increased in ionomycin-treated cells compared to the controls, rapidly. The relative intensities of MitoSOX also significantly increased in ionomycin-treated cells compared to the controls. However, the time point was different compared to Fluo-4AM assay. Finally, we checked mitochondrial membrane oxidations. Treatment with an ionomycin significantly increased fluorescent emissions of mitochondrial membrane oxidations compared to the controls. These results show that treatment with a low concentration of ionomycin induced neurite degeneration via mitochondrial oxidation, and one reason of its phenomena may be depend on the influx of calcium ion into the intracellular region. Neurite degeneration is well known in a development and a progression of severe neurodegenerative disorders. These phenomena via calcium-related pathway impact on the onset of neurodegenerative disorders.

Disclosures: **K. Fukui:** None. **S. Nakamura:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.06/X5

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: JSPS KAKENHI 26460709, 17K09045

Title: Mitochondrial functions of 4-nitrophenylphophatase domain and non-neuronal SNAP25-like protein homolog 1 in mouse dorsal root ganglion neurons

Authors: *E. OKUDA-ASHITAKA, E. MATSUOKA, I. OHTSU, Y. YANO
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Abstract: 4-Nitrophenylphosphatase domain and non-neuronal SNAP25-like protein homolog (NIPSNAP) 1 is expressed in the synaptic membrane and the mitochondria. Synaptic NIPSNAP1, which interacts with the neuropeptide nocistatin, has been implicated in the inhibition of tactile pain allodynia. On the other hand, in the mitochondria, NIPSNAP1 presents in the matrix and the inner membrane, and it binds several protein, including amyloid precursor protein, mitochondrial matrix chaperone heat shock protein 60, and the E2 component of mitochondrial branched-chain α-keto acid dehydrogenase enzyme complex. However, the effects of NIPSNAP1 on mitochondrial functions remain unclear. Here, we investigated the involvement of NIPSNAP1 in the mitochondrial functions in the dorsal root ganglion (DRG) neurons prepared from NIPSNAP1-deficient mice.
The cellular ATP content was only slightly increased in the NIPSNAP1-deficient DRG cells, as determined using a luciferase-based luminescence assay. The level of reactive oxygen species (ROS) production, which was determined by dihydroethidium staining, was found to increase approximately 4-fold in NIPSNAP1-deficient cells, which was equivalent to the increase in the wild-type cells treated with a mitochondrial uncoupler, carbonyl cyanide m-chlorophenyl hydrazine (CCCP). The level of LC3-II, an autophagosome-associated form of the protein, was increased in the NIPSNAP1-deficent cells. Furthermore, NIPSNAP1 deficiency induced a significant increase and punctate arrangement of p62, an autophagosome substrate, which localized with the mitochondria. CCCP increased the intensity of this punctate arrangement of p62 and the subsequent colocalization of the mitochondria with lysosomal-associated membrane protein-1, in the wild-type cells, whereas the colocalization with the lysosome disappeared in the NIPSNAP1-deficent cells. These results suggest that NIPSNAP1 is involved in the regulation of ROS production and the autophagy of the mitochondria in DRG neurons.

Disclosures: **E. Okuda-Ashitaka:** None. **E. Matsuoka:** None. **I. Ohtsu:** None. **Y. Yano:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.07/X6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Marato-TV3 20141430

Title: Increased mitochondrion fusion and mobility in ApoE4-harboring astrocytes

Authors: R. LARRAMONA[1], C. COBOS[1], A. GOLBANO[1], C. MENACHO[1], A. ERASO-PICHOT[1], J. X. COMELLA[2], A. GUTIERREZ[3], J. VITORICA[4], R. MASGRAU[1], *E. GALEA[5,6]
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Abstract: Background: Apolipoproteins (ApoE) are cholesterol carriers that in humans exist in three alleles: E2, E3 and E4. ApoE4 is the most important genetic risk factor in late onset Alzheimer´s disease (LOAD)— particularly affecting women—but its pathogenic mechanism remains unclear. The novelty of our approach is: 1) we focus on the pathological actions of *endogenous* ApoE4 in astrocytes, the cells that produce most of ApoE in the brain; and 2) we aim to link mitochondrial dysfunction, a hallmark and biomarker of LOAD, with ApoE4-elicited astrocyte dysfunction. Specifically, a decrease in mitochondrial DNA (mitDNA) contents has been detected in cerebrospinal fluid (CSF) of patients at early stages of LOAD, particularly in ApoE4 carriers (*Podlesniy et al. Annals of Neurology 74:655668, 2013*). The decreased CSF mitDNA suggests alteration of mitochondrial fusion, fission and mitophagy, which are essential to keep mitochondria healthy. We seek to determine whether impaired mitochondrial dynamics in ApoE4 carriers originate in astrocytes. Methods: For proof of concept, we used immortalized astrocytes expressing human ApoE isoforms. Mitochondrion dynamics were assessed by computerized morphometry (Image J), and by measurements of squared displacement (D^2 , Imaris) of mitochondria stained with MitoTracker. Molecules that regulate mitochondrial fusion/fission, kinesis and mitophagy were examined by qPCR and Western blots. ATP and lactate were assessed as bioenergetics markers. Results: As compared to ApoE3 astrocytes, ApoE4 astrocytes showed: 1) defective fission, as evidenced by increased network contents in cells challenged by stimuli that fragment mitochondria such as oligomycin; 2) greater D^2 , suggesting increased motility; 3) reduced ATP and increased lactate production, suggesting

impairment of mitochondrial respiration and activation of compensatory glycolysis, and 4) decreased PARKIN, a protein key to mitophagy; and 5) increased expression of *Miro* mRNA—which encodes for a protein that regulates mitochondrial motility. Conclusions: ApoE4-harboring astrocytes may present hyperfusion and hypermotility associated with impaired energetics and altered mitophagy. Ongoing work is aimed to: 1) understand why ApoE4 impairs mitochondrion dynamics in astrocytes; 2) confirm *in vitro* observations in ApoE4 mouse and human brains, and 3) assess whether the decrease in mitDNA concentration in CSF of LOAD patients correlates with altered contents of proteins related to mitophagy and motility; the overarching goal is to generate an astrocyte-based mitochondrion signature of early LOAD.
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Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.08/X7

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS067078

NIH Grant NS034179

Title: Deletion of the mitochondrial protein prohibitin in neurons leads to mitochondrial dysfunction and impaired autophagy

Authors: L. QIAN[1], C. J. ANDERSON[1], G. MANFREDI[1], C. IADECOLA[1], *P. ZHOU[2]
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Abstract: Prohibitin (PHB) has recently emerged as a key modulator of mitochondrial function. We have demonstrated that PHB upregulation provides strong neuroprotection in several injury modalities including cerebral ischemia (J. Neurosci., 32:583, 2012, Stroke 45:1131, 2014). However, it remains unclear whether PHB deletion specifically in neurons affects their survival and, if so, through which mechanisms. To address this question we used the cre/-lox system to delete PHB in neuronal cultures. PHB flox/flox neurons were cultured from E16 mouse embryos. At 1 day in vitro (DIV), a cre lentivirus (cre) under a CMV promoter or vector (control) was added to initiate PHB deletion. Cell viability was assessed by morphological criteria and the MTT assay. Mitochondrial membrane potential (TMRM fluorescence imaging), mitochondrial

morphology (MitoDsRed imaging), OPA1 processing (Western blotting), and autophagy (LC3-II and p62) were also analyzed. Cre mediated PHB deletion was complete 3 days after recombination, and PHB protein started decline at 3DIV and was maximal at 7DIV. No changes in cell morphology, MTT and ATP levels were noticed in cre-treated neurons until 9DIV, but at 14DIV all cells were dead. Next, we analyzed mitochondrial function and autophagy in cre cultures at 7 days, when PHB protein is low but cells are still viable. At this time, there was a small but significant mitochondrial membrane potential drop in cre treated cells (836±27 RFI units) compared to controls (971±32, $p<0.05$, n=3). Many of these cells had fragmented mitochondria (cre: 49±8%; controls: 19±5%, $p<0.05$), associated with processing of the long isoform of OPA1, a mitochondrial inner membrane protein involved in fusion and maintaining cristae structure. We then assessed the role of PHB deletion in autophagy. We found that LC3II and p62, well-characterized autophagy markers, are significantly lower in cre-treated cells (normalized protein band intensity LC3II: 4.8±0.3, p62: 1.6±0.1) than in controls (LC3II: 6.3±6, p62: 1.8±0.06, n=6, $p<0.05$), suggesting impaired autophagy. We conclude that PHB is involved in maintaining normal mitochondrial function and neuronal autophagy. Disruption of PHB expression will lead to mitochondrial dysfunction and autophagy impairment, contributing to neurodegeneration.

Disclosures: L. Qian: None. **C.J. Anderson:** None. **G. Manfredi:** None. **C. Iadecola:** None. **P. Zhou:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.09/X8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH UF1 AG046148 to RDB

Alzheimer's Drug Discovery Foundation (ADDF) to RDB

Title: Alzheimer's disease clinical trial recruitment and retention model in the Greater Los Angeles area

Authors: *R. W. IRWIN[1], G. HERNANDEZ[2], C. M. SOLINSKY[3], C. M. LOPEZ[4], N. KONO[5], W. J. MACK[5], L. S. SCHNEIDER[5], R. D. BRINTON[6]
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Abstract: Recruitment and retention of early Alzheimer's patients in clinical trials provide both challenges and opportunities for improvement (Watson, 2012). To expedite recruitment of 24 participants at a single clinical site for NCT02221622 we sought to move past traditional recruitment approaches of physician referrals. We discuss innovative methods to recruit, retain, and budget for an early phase trial in a university setting. Recruitment materials included paper and web-based flyers, social media, health fairs, and radio advertisements (3 local radio stations). All recruitment materials were approved by IRB. Qualified staff with current protected health information compliance certificates conducted phone pre-screens and entered caller information into a secure REDCap database. The Clinical Study Coordinator called potential volunteers for follow-up phone interviews, scheduled screening visits, and maintained communication throughout the trial. Many participants (55%) opted to use taxi transportation that allowed real-time smartphone GPS tracking for both the caregivers and clinicians, improving appointment efficiency and reducing uncertainty. Only reimbursements for transportation and parking costs were afforded in the recruitment process. The trial was conducted at USC and funded by NIH-NIA and ADDF. Of the recruitment materials used, radio advertisements proved most effective in Greater Los Angeles. Radio Station: KUSC (11.8%), KNX (86.3%), KOST (0.0%), Other (2.0%). Self-referral: Yes (45.7%), No (54.3%). Age range: 56-91, mean 71.47 +/-10.19. Previous diagnosis of dementia: Yes (48.8%), No (51.2%). Study Partner available: Yes (92.3%), No (7.7%). Previous MRI: Yes (42.1%), No (42.1%), Maybe (15.8%). Pre-screen results: Pass (31.6%), Fail (17.1%), Declined to participate (17.1%), Called for information only (34.2%). Of those that passed pre-screen inclusion/exclusion criteria, 47% of those screened at clinic were enrolled with acceptable MRI results and MMSE >20. Of those enrolled there was one dropout. We developed an effective recruitment framework to enroll 24 volunteers with early Alzheimer's disease into a double-blind placebo controlled phase-1b study to test the safety of once-per-week intravenous Allopregnanolone, a candidate regenerative therapeutic. The recruitment funnel was most effective through brief radio advertisements followed by prescreening interviews and medical record review to recruit and retain willing volunteers. Our recruitment strategy utilized local radio announcements and convenient ride-share transportation and serves as an innovative model for efficient clinical trial recruitment.

Disclosures: **R.W. Irwin:** None. **G. Hernandez:** None. **C.M. Solinsky:** None. **C.M. Lopez:** None. **N. Kono:** None. **W.J. Mack:** None. **L.S. Schneider:** None. **R.D. Brinton:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.10/X9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA P01AG026572

Alzheimer's Association SAGA-17- 419459

Paul Slavic Trust

Title: Evaluating sex- and apoe genotype dependent response to allopregnanolone treatment

Authors: *M. K. DESAI[1], R. W. IRWIN[2], M. PRAJAPATI[3], R. D. BRINTON[5,4]
[1]Clin. Pharm. and Pharmaceut. Econ. & Policy, [2]Pharmacol. and Pharmaceut. Sci., [4]Sch. of Pharm., [3]USC, Los Angeles, CA; [5]Ctr. for Innovation in Brain Sci. and Dept. of Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: Currently there is no therapeutic intervention to prevent, cure or delay the progression of Alzheimer's disease (AD). The ApoE4 allele, present in ~20% of the population, increases the risk for AD but affects women and men differently. While males heterozygous for ApoE4 have hardly any increased risk of AD compared with males that are ApoE4 negative, ApoE4 substantially increases AD risk in females. In the present study, we aimed to compare the efficacy of allopregnanolone (Allo), an neuroregenerative therapeutic, in male and female mice with different ApoE status. ApoE3, ApoE4 and ApoE3/4 mice were subjected to a weekly intramuscular injection of Allo (1.5 mg/mL) at 2 mg/kg dose or saline for 26 weeks starting from 10 months of age. The dose, formulation and duration of treatment were chosen to reflect the Phase 1b/2a clinical trial of Allo, currently in progress (ClinicalTrials.gov ID: NCT02221622). We have completed novel object recognition (NOR) testing on these mice and intend to carry out further analyses using biochemical, metabolomic and next-generation sequencing techniques. Results of the behavior study demonstrate that while Allo benefits both ApoE3 and ApoE4 males and females, Allo-treated ApoE4 mice have much higher discrimination index (DI) scores compared to their ApoE3 counterparts. There were no significant differences in the body weight or food intake between the Allo-treated and control animals. We are currently conducting transcriptomic analyses of the hippocampi from these mice to reveal the underlying mechanisms of Allo-induced neuroregeneration, and their interaction with sex and ApoE background. Plasma-based metabolomics data from mice will be compared to human metabolomics data from participants of the ongoing clinical trial. Characterization of the lipidomic profile in the plasma of these mice will elucidate Allo's role as a modulator of lipid metabolism and AD pathogenesis, considering ApoE4 being responsible for abnormal lipid profile and dysregulated cholesterol metabolism in AD. While its neuroregenerative therapeutic potential has been repeatedly demonstrated, this is the first time Allo is being tested in a targeted genotype, as an ongoing effort to promote precision medicine in AD patients and at-risk populations with different sexes and genetic background. This work was supported by NIA P01AG026572, Alzheimer's Association SAGA-17-419459 and Paul Slavic Trust to RDB.

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Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA U01AG031115

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NIH/NIA Grant P50 AG16573

USC Provost Fellowship

CIRM Predoctoral Research Traineeship

Title: Development of an iPSC based biomarker strategy to identify neuro-regenerative and mitochondrial responders to Allopregnanolone

Authors: *C. M. SOLINSKY[1], J. A. PARK[4], H. C. CHUI[2], M. BLURTON-JONES[5], J. ICHIDA[2], R. D. BRINTON[6,3]
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Abstract: Alzheimer’s disease (AD) is a national and global epidemic with complex pathoetiology including compromised brain metabolic activity and decreased regenerative capacity. Allopregnanolone (Allo) is an investigational neuroregenerative therapeutic, currently in Phase 1b clinical trial for AD (NCT02221622, https://clinicaltrials.gov/ct2/show/NCT02221622?term=NCT02221622&rank=1). In rodent preclinical models, Allo promotes neural stem cell (NSC) proliferation and neural differentiation and improves mitochondrial function. To develop biomarkers to predict regenerative response to Allo, we have initiated proof of concept analyses to determine the impact of Allo on human induced pluripotent stem cells (iPSCs) and iPSC-derived neural cells. T-cells from Allo clinical trial participants were reprogrammed via a non-integrating, non-viral method, to iPSCs. Additional iPSCs were provided by the University of California Irvine Alzheimer’s Disease Research Center (UCI-ADRC) and the Institute for Memory Impairments and Neurological

Disorders. Using dual inhibition of SMAD signaling, iPSCs were differentiated to NSCs. Analyses were conducted to determine the regenerative and bioenergetic effect of Allo on clinical trial participant iPS-derived NSCs. Mitochondrial respiration and regenerative capacity were determined by metabolic analyzer and flow cytometry evaluation of EdU incorporation respectively. Within the cell lines of the first dose cohort of clinical trial participants, after in vitro Allo treatment, 40% had increased NSC proliferation (mean increase 14% versus vehicle) and bioenergetic capacity (mean increase 13% versus vehicle). These participant cell lines have been labeled 'responders', while those that did not have increased NSC proliferation or metabolic capacity are 'non-responders'. These data demonstrate that Allo promotes regeneration and mitochondrial function of iPSC-derived NSCs in a subset of clinical trial participants. In order to translate these in vitro data to clinical relevance, the next step is to analyze the cell data for correlations with the clinical trial cognitive and imaging data as well as single nucleotide polymorphism analysis to identify potential genetic markers of responders versus non-responders. These data form the foundation for developing the first biomarker of regenerative potential in brain to determine and monitor response to allopregnanolone as a regenerative therapeutic.

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Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.12/X11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AGO33288

Title: Pharmacokinetics and safety profile of a single-dose administration of an estrogen receptor β-selective phytoestrogenic formulation (PhytoSERM) in peri and postmenopausal women

Authors: *G. D. HERNANDEZ[1], ***G. D. HERNANDEZ**[1], L. ZHAO[5], Y.-L. CHEN[2], A. FRANKE[6], W. J. MACK[2], L. S. SCHNEIDER[3], R. D. BRINTON[4]
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Abstract: Background: Of all victims of Alzheimer's disease (AD) 68% are postmenopausal women. Estrogen and hormone replacement therapies (HRT) begun at the time of menopause transition have been associated with reduced risk and delayed onset of AD. However, adverse outcomes of HRT have led to an increasing number of women declining its use but seeking non-pharmaceutical alternatives. The search for a safe approach to promote estrogenic signaling in

the brain, without eliciting adverse effects, has focused on the development of tissue-selective estrogen receptor modulators (SERMs). Selective estrogen receptor-β (ER-β) targeting has been attempted in the development of therapies for a range of conditions including cognitive impairment and menopausal symptoms. PhytoSERM, a preparation of genistein, daidzein, and S-equol, has an 83-fold selective affinity for (ER-β) and may promote neuronal survival and estrogenic mechanisms in the brain without having feminizing activity in the periphery.
Objective: To assess the safety, tolerability and single-dose pharmacokinetics of the phytoSERM formulation in peri- and postmenopausal women.
Methods: Eighteen women aged 45-60 years from a 12-week clinical trial evaluating cognitive performance and vasomotor symptoms were randomly assigned to placebo, 50mg, or 100mg phytoSERM treatment groups. Plasma levels of the 3 parent phytoestrogens and their metabolites were measured before and at 2, 4, 6, 8 and 24 hours after ingestion by isotope dilution HPLC electrospray ionization tandem mass spectrometry.
Results: Plasma concentrations of genistein, daidzein and S-equol peaked at 9, 6 and 4 h, respectively for the 50mg dose, and at 6, 6 and 5 h, respectively for the 100 mg dose. The maximum concentration (C_{max}) and area under the curve (AUC) for the 3 parent compounds were greater in the 100 mg dose group indicating a dose-dependent change in concentration with the phytoSERM treatment. No adverse events were elicited.
Conclusion: The phytoSERM combination was well tolerated, appeared without adverse effects, and exhibited a favorable pharmacokinetic profile. After single oral administration of 50 and 100mg tablets of the phytoSERM formulation, the phytoestrogens genistein, daidzein and S-equol were rapidly absorbed, reached high plasma concentrations, and showed a dose proportional increase in concentration exposures in its pharmacokinetics. The formulation may prove to be advantageous in future clinical trials for several peri- and postmenopausal conditions.

Disclosures: G.D. Hernandez: None. **L. Zhao:** None. **Y. Chen:** None. **A. Franke:** None. **W.J. Mack:** None. **L.S. Schneider:** None. **R.D. Brinton:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.13/X12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant UO1 AG047222

Kenneth T and Eileen L. Norris Foundation

Title: Impact of allopregnanolone on the differentiation of neural stem cell

Authors: *S. CHEN[1,2], J. YAO[2], K. WONG[2], R. D. BRINTON[1,2]
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Abstract: Previous studies demonstrated that the endogenous steroid allopregnanolone promotes proliferation of both human and rodent neural stem cells (NSCs) *in vitro* and *in vivo* in the triple transgenic mouse model of Alzheimer's disease (3xTgAD). In this study, we aimed to investigate the impact of allopregnanolone on neural differentiation. We first assessed the effect of aging and Alzheimer's-associated genotype on the differentiative capacity of adult NSCs from 3xTgAD mice. NSCs from 3-, 6- and 15-month 3xTgAD and non-transgenic mice were cultured and their differentiation capacity was determined. We demonstrated that there is an age- and Alzheimer's gene-dependent decrease in overall NSCs differentiation accompanied by a shift from neuronal to glial differentiation. Allopregnanolone treatment significantly increased the ratio of MAP2-positive-neurons to GFAP-positive-astrocytes in adult mouse NSCs, in consistency with our findings in allopregnanolone-treated embryonic rat NSCs. The *in vivo* efficacy of allopregnanolone to prevent or reverse the loss of neuronal differentiative capacity was investigated in 5-month-old male 3xTgAD mice. Flow cytometry-based analysis indicated that allopregnanolone increased the number of newly generated neurons as indicated by the increase in the number of BrdU positive, and BrdU/NeuN double positive cells. Allopregnanolone also upregulated the expression of neural proliferation marker, PCNA, and the immature neuronal marker, doublecortin, which was further confirmed by immunohistochemistry labeling. In addition, the expression of Olig2, an oligodendrocyte precursor cell marker, was also increased by allopregnanolone treatment, supported by immunohistochemistry analyses where increased distribution of Olig2 positive cells were found in the corpus callosum area in the brain. Interestingly, the increased differentiation in neuronal cell and oligodendrocyte precursor is in parallel with an increase of expression in insulin-like growth factor-1 (IGF-1) and IGF-1 receptor (IGF-1R). To explore the underlying mechanisms of allopregnanolone-induced neural differentiation and the involvement of the insulin/IGF-1 pathway, we are currently investigating the activation and expression of AKT, a key node in IGF-1/IGF-1R signaling cascade. Collectively, these findings suggest that allopregnanolone is a regenerative therapeutic candidate that could be capable to prevent or delay neurogenic deficits associated with Alzheimer's disease.

Disclosures: S. Chen: None. **J. Yao:** None. **K. Wong:** None. **R.D. Brinton:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.14/X13

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: AHA fellowship16PRE29560003

AHA Grant in Aid 17GRNT33410181

NIH Grant NS096987

Title: Zn^{2+}-induced mitochondrial dysfunction: Dependence upon disruption of buffering, synergism with Ca^{2+} and contributions to neuronal injury *In vitro* and *In vivo*

Authors: *S. G. JI[1], Y. V. MEDVEDEVA[2], H. Z. YIN[2], J. H. WEISS[2]
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Abstract: Ca^{2+} and Zn^{2+} contribute critically to the induction of acute ischemic neurodegeneration. Zn^{2+} is released at synapses, where it can enter postsynaptic neurons. There are also intracellular Zn^{2+} pools bound to buffering proteins, which can be released during ischemia. Prior studies found Zn^{2+} to potently disrupt mitochondrial function, suggesting that these organelles may be important targets of its effects. Yet key pertinent questions remain.
(1) Quantitative relationship between mitochondrial Zn^{2+} loading and its effects. Most prior studies have used exogenous Zn^{2+} exposures to study the effects of mitochondrial Zn^{2+} accumulation, but the quantitative relationship between cytosolic buffering, mitochondrial Zn^{2+} uptake and dysfunction has been little examined. Using a combination of exogenous Zn^{2+} exposure and graded disruption of intracellular buffering on cultured neurons, we found that while brief 300 µM Zn^{2+}/90 mM K^+ exposures (to trigger entry through voltage gated Ca^{2+} channels [VGCC]), caused modest mitochondrial dysfunction, with disrupted buffering, substantial effects occurred with far lower Zn^{2+} exposures.
(2) Synergy of Zn^{2+} effects with Ca^{2+}. As most studies of Zn^{2+} have been done in Ca^{2+}-free conditions, it is critical to examine how Ca^{2+} impacts the effects of Zn^{2+} on mitochondria to better model its roles in pathophysiologic conditions. We found that while mitochondrial Zn^{2+} uptake through VGCC was attenuated in the presence of Ca^{2+}, its impact on mitochondrial function was significantly increased, suggesting strong synergy between Ca^{2+} and Zn^{2+} despite reduced accumulation.
(3) Mitochondrial calcium uniporter (MCU) and interventions. Zn^{2+} entry through the MCU contributes to its effects. We are presently examining the dependence of these effects upon the MCU, and the ability of interventions delivered after the Zn^{2+} exposure to reverse mitochondrial dysfunction and improve cell survival.
(4) Mitochondrial Zn^{2+} in ischemic neurodegeneration. Using hippocampal slices and *in vivo* rat cardiac arrest models, we have begun examining how mitochondrial accumulation of endogenous Zn^{2+} may contribute to *in vivo* ischemic injury. We found that differential vulnerabilities of CA1 and CA3 hippocampal pyramidal neurons may in part reflect differences in their handling of mitochondrial Zn^{2+}. Furthermore, preliminary *in vivo* studies provide evidence for early mitochondrial Zn^{2+} accumulation in many injured neurons after transient ischemia.
Present studies lend further support to a role of mitochondrial Zn^{2+} accumulation in neurodegeneration; we hope ongoing work will suggest new approaches for therapeutic interventions.

Disclosures: **S.G. Ji:** None. **Y.V. Medvedeva:** None. **H.Z. Yin:** None. **J.H. Weiss:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.15/X14

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Targeting mitochondrial fission for neuroprotection in peripheral diabetic neuropathy

Authors: *Y. LIU[1], K. FLIPPO[1], R. A. MERRILL[1], M. YOREK[2], G. PERKINS[3], Y. USACHEV[1], S. STRACK[1]
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Abstract: Diabetes has become a fully-blown epidemic requiring global attention. WHO reported that 422 million people currently living with the disease and it is estimated to become the 7th leading cause of death in 2045. Presenting with loss of sensation and chronic pain, peripheral diabetic neuropathy (PDN) is a debilitating comorbidity affecting at least 50% of the diabetic patient population. With palliative care being the only option now, there is an urgent need of innovative therapies for PDN. Emerging evidence recently indicated compromised mitochondria structure and function in diabetes without a clear understanding of underlying mechanism. Mitochondria forms highly dynamic networks that constantly undergoing the process of fission and fusion, governed by the dynamin family of large GTPases. Balanced fission and fusion are required for proper function of mitochondria. Interestingly, excessive mitochondrial fission was implicated in many neurodegenerative disorders including Alzheimer's and Huntington's diseases. Therefore, we investigated whether targeting mitochondrial fission can be a potential therapeutic strategy for PDN. Dynamin-related protein 1 (Drp1) is an essential mitochondrial fission enzyme activated by dephosphorylation via two phosphatases including calcineurin and a neuron-specific, mitochondria localized isoform of protein phosphatase 2A containing the Bβ2 regulatory subunit (PP2A/Bβ2). We generated the Bβ2 knock-out (KO) mouse in which we observed elongated mitochondria in neurons as well as reduced high-glucose induced superoxide production in their DRG neurons. Bβ2 deletion increased mitochondrial length and axonal localization, while preventing axonal mitochondrial fission and depletion in sciatic nerve in the STZ model of type-1 diabetes. These animals were shown to be protected from thermal hypoalgesia. Moreover, KO of Bβ2 also provided protection from both thermal and mechanical hypoalgesia as well as impaired nerve conductivity in the db/db mouse model of type-2 diabetes. Taken together, our preliminary data showed that Bβ2 KO animals are resistant to PDN in both type-1 and type-2 diabetes models. Hence, targeting

mitochondrial fission through PP2A/Bβ2 may provide new strategies for the treatment of diabetic neuropathies.

Disclosures: Y. Liu: None. **K. Flippo:** None. **R.A. Merrill:** None. **M. Yorek:** None. **G. Perkins:** None. **Y. Usachev:** None. **S. Strack:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.16/X15

Topic: C.01. Brain Wellness and Aging

Support: AFI #14838

Title: Mediterranean diet and physical activity improve the age dependent decrease in mRNA expression of genes of mitochondrial function in NMRI mice

Authors: *C. V. SILAIDOS, H. ASSEBURG, S. HAGL, G. ECKERT
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Abstract: Mitochondrial dysfunction (MD) represents a key factor in brain aging and neurodegenerative diseases (ND) including decreased mitochondrial respiration and ATP levels. Therefore MD is a promising target for nutritional prevention strategies. Recent studies confirm that physical and cognitive activity combined with the Mediterranean diet is associated with a decreased risk for dementia. Therefore this study aimed to investigate effects of a grape seed extract and a natural *Extract* of Olive Mill Waste Water (Group RO) combined with physical activity (group ROEn) on mitochondrial function of aged NMRI mice. Male mice were fed for 6 month comparing mitochondrial function with 3-month old mice (group YC) and to old matched (19-month) control-fed mice (group OC). mRNA expression analysis was conducted using brain tissue focusing on genes playing a role for mitochondrial function and for hormesis. The expression rates were calculated in relation to the young control group (100%). Gene expression analysis of complex I and IV of the respiratory chain revealed a non significant decrease in complex I expression in the aged group and a significant increase in the RO and ROEn group (104,6%;106,9%). The complex IV expression of the OC group was significant lower than in the YC group (69,2%). Through the intervention the expression increased significantly for the RO (90,9%) and for the ROEn (96%) group. Significantly decreased of gene expression of PGC1α, CREB, and Synaptophysin 1 was detected in OC in comparison to the YC group whereas BNDF levels were unchanged. The decreased mRNA expression was reversed in the RO and ROEn intervention groups. An aged-dependent decrease in gene expression was also found for AMPK and for the sirtuines Sirt1 and Sirt3. The RO and the ROEn intervention increased the Sirt3 expression (103% and 98,8%, respectively). The ROEn intervention showed a higher Sirt1 and

AMPK expression compared to the OC group. In conclusion, components of the Mediterranean diet in combination with physical activity appears to be a successful approach to improve or prevent the age dependent decrease in gene expression of genes which are associated with mitochondrial function and hormesis. (Supported by the Alzheimer Forschung Inititative e.V.; AFI #14838).

Disclosures: **C.V. Silaidos:** None. **H. Asseburg:** None. **S. Hagl:** None. **G. Eckert:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.17/X16

Topic: C.01. Brain Wellness and Aging

Support: BMBF #031A590C

Title: Purified olive polyphenols improve mitochondrial dysfunction in a cell model of early Alzheimer´s disease

Authors: *R. GREWAL[1], J. VOLK[2], A. SARAFEDDINOV[3], J. ZOTZEL[3], S. MARX[3], J. TRETZEL[3], H. WARZECHA[2], G. ECKERT[1]
[1]Inst. Fuer Ernaehrung In Praevention Und Therap, Giessen, Germany; [2]Technische Univ. Darmstadt, Darmstadt, Germany; [3]N-Zyme BioTec GmbH, Darmstadt, Germany

Abstract: As components of the Mediterranean diet olive polyphenols may play a crucial rule for the prevention of Alzheimer`s disease (AD). Since, mitochondrial dysfunction plays a major role in both, brain aging and early AD, effects of different highly purified phenolic secoiridoids were tested on mitochondrial function in SH-SY5Y-APP cells - a cellular model of early AD. SH-SY5Y-APP cells were incubated with Hydroxytyrosol, Tyrosol, Oleacein, Oleurosid, Oleuropein and Oleocanthal which were obtained in a novel biotechnological and preparative approach, for 24h, or pre-incubated for 1h and insulted with the complex I - inhibitor Rotenon, for 24h. All tested secoiridoids significantly increased basal ATP levels. For advanced testing the best compounds were selected for high-resolution respirometry using an Oxygraph-2k (Innsbruck, Austria). Oleacein and Oleocanthal (0.05 µM each) showed a significant elevated endogenous mitochondrial respiration. In addition, Oleocanthal lead to an increase in complex l activity, as well as in OXPHOS and ETS respiratory states. To investigate the underlying molecular mechanisms the expression of genes associated with mitochondrial biogenesis, respiration, dynamics, and synaptic plasticity (PGC1α, SIRT, AMPK, CREB, Nrf1, Tfam, complex l, lV and V, Drp1, Mfn1, Opa1) are currently under investigation. So far, the findings have especially identified Oleocanthal as promising olive compound to prevent Alzheimer´s

disease in an early state. (Supported by the German Ministry of Education and Research; BMBF #031A590C)

Disclosures: R. Grewal: None. **J. Volk:** None. **A. Sarafeddinov:** None. **J. Zotzel:** None. **S. Marx:** None. **J. Tretzel:** None. **H. Warzecha:** None. **G. Eckert:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.18/X17

Topic: C.01. Brain Wellness and Aging

Support: BMBF #031A590C

Title: Effects of long-term treatment with purified olive secoiridoids improve cognition and mitochondrial dysfunction in aged NMRI mice

Authors: *M. REUTZEL[1], R. GREWAL[1], C. SCHAEFER[1], J. VOLK[2], A. SARAFEDDINOV[3], J. ZOTZEL[3], S. MARX[3], J. TRETZEL[3], H. WARZECHA[2,3], G. ECKERT[1]
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Abstract: As components of the Mediterranean diet olive polyphenols may play a crucial role for the prevention of Alzheimer`s disease (AD). Since, mitochondrial dysfunction plays a major role in both, brain aging and early AD the effects of mixture of highly purified olive secoiridoids (24.7 % hydroxytyrosol, elenolic acid derivates 10.5 %, oleacein 14.6 %, oleuropein 7.2 %, oleuropein aglycone 36.7 %, and oleurosid 6.2 %) were tested on mitochondrial function and behavioral performance in a mouse model of brain aging. Over 6 months female NMRI mice (12 months of age) were fed with the polyphenol-rich extract (13.75 mg/kg b.w.; manufactured by N-Zyme BioTec GmbH, Darmstadt, Germany) or a modified, study diet (C1000; Altromin, Lage, Germany). C1000 fed 3 month old mice served as young control.
Mice were behaviorally tested at the beginning and at the end of the feeding study. After 6 months, ATP-levels were measured in dissociated brain cells (DBC's). In contrast to young mice, aged control mice showed significant reduced willingness to explore new environment in the Y-Maze-test. The dietary supplementation with secoiridoids strongly improved the short-term memory and locomotor activity of aged mice. Even the long-term memory was slightly increased after 6 months of supplementation as elaborated in the Passive Avoidance-test. Secoiridoid-fed mice showed significant increased ATP-level which almost compensated for age related mitochondrial dysfunction. Our results so far show that a high purified polyphenol-rich diet has positive long-term effects on cognition and energy metabolism in the brain. To investigate the underlying molecular mechanisms, the expression of genes associated with

mitochondrial biogenesis, respiration, dynamics, and synaptic plasticity (PGC1α, SIRT, AMPK, CREB, Nrf1, Tfam, complex l, lV and V, Drp1, Mfn1, Opa1) are currently under investigation. (Supported by the German Ministry of Education and Research; BMBF #031A590C)

Disclosures: **M. Reutzel:** None. **R. Grewal:** None. **C. Schaefer:** None. **J. Volk:** None. **A. Sarafeddinov:** None. **J. Zotzel:** None. **S. Marx:** None. **J. Tretzel:** None. **H. Warzecha:** None. **G. Eckert:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.19/X18

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant

Title: Molecular composition and regulation of mitochondrial permeability transition pore

Authors: *N. MNATSAKANYAN, H.-A. PARK, J. WU, L. R. CLIFFORD, P. MIRANDA, E. A. JONAS
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Abstract: The mitochondrial permeability transition (mPT) is the main cell death pathway during neurodegenerative diseases, traumatic brain injury and stroke. The opening of the mitochondrial permeability transition pore (mPTP) occurs during mitochondrial Ca^{+2} overload accompanied by oxidative stress and adenine nucleotide depletion. While the molecular nature and composition of mPTP remain controversial, its regulation and pharmacology have been well studied. We have recently characterized a novel large conductance ion channel located in the membrane-embedded c-ring of F_1F_o ATP synthase, which we suggest, based on its biophysical and pharmacological properties, to form the pore of mPT. We have over-expressed and purified recombinant human c-subunit from different host cells and demonstrated that it forms a voltage-gated channel with ~100 pS average conductance as a subconductance state and up to ~1.5-2 nS peak conductance. The c-subunit is a part of the membrane-embedded F_o subcomplex, which tightly interacts with the soluble F_1 portion of ATP synthase. We have now shown that the stoichiometric ratio between the c-subunit ring and the F_1 subunits is crucial for closing the c-subunit leak channel and for increasing the bioenergetic efficiency of mitochondria. We are currently studying the ATP synthase structure and the conformational re-arrangements necessary for c-subunit gating. We are also investigating the role of the c-subunit leak channel in neuronal death and survival and its regulation by different pharmacological agents. These findings will provide us with increased understanding of the role of mPTP in aging and neurodegeneration.

Disclosures: **N. Mnatsakanyan:** None. **H. Park:** None. **J. Wu:** None. **L.R. Clifford:** None. **P. Miranda:** None. **E.A. Jonas:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.20/X19

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Exploration of mitochondrial bioenergetics using human iPSC-derived neurons

Authors: K. KIM, N. AOYAMA, K. MANGAN, M. HANCOCK, *C. B. CARLSON
Cell. Dynamics Intl., Madison, WI

Abstract: The advent of induced pluripotent stem cell (iPSC) technology now grants the scientific community access to previously unattainable human cell types, specifically those from the brain. Moreover, iPSC technology enables us to compare cells from apparently healthy normal individuals to those cell types from disease-specific and patient-derived samples. Neurological and neurodegenerative disorders are a global health concern. Many of these disease pathologies are thought to be driven by dysfunctional mitochondria creating an imbalance in cellular bioenergetics. The ability to measure discrete changes in cellular energy and metabolism in a real-time, label-free approach is possible with Seahorse XF technology. We have used this instrument to assess the impact of numerous conditions (ranging from neuronal culture medium, time in culture, cell density, mitochondrial stress agents, and genetic mutations) on the bioenergetics profile human iPSC-derived cell types. Here we focus on development of the methods and protocols to evaluate mitochondrial stress in GABAergic, glutamatergic, dopaminergic, and motor neurons. Additionally, we have tested iPSC-derived astrocytes, macrophages, and skeletal muscle as each of these cell types are possibilities for co-culture to generate more complex and biologically relevant cell models. Finally, establishing baseline assay signals for these various cell types derived from apparently healthy normal donors paves the way for disease modeling. Examples of neurons and astrocytes with the SOD1 G93A mutation will be presented.

Disclosures: **K. Kim:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **N. Aoyama:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **K. Mangan:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **M. Hancock:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **C.B. Carlson:** A. Employment/Salary (full or part-time):; Cellular Dynamics International.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.21/X20

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: DC013073

Kiwanis Foundation

Title: Quantifying brain susceptibility to metabolic stress using autofluoresence in mouse brain slices

Authors: *K. STEBBINGS, K. MURPHY, K. ZWONITZER, D. LLANO
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Abstract: Taking advantage of the natural auto-fluorescence of the cell's main energy carrying molecules, FAD^{2+} and NADH, we have created methods which can quantitatively assess the sensitivity of brain tissue metabolism to low oxygen (hypoxic) and oxidative stress. The ratio of the imaged fluorescence of oxidized FAD^{2+} to reduced NADH is known as the redox ratio or redox potential and changes characteristically with both types of stress. Slice imaging allows us to test deeper structures than is possible even with advanced in-vivo imaging techniques and can more accurately quantitate the relative sensitivity of different areas of the brain simultaneously. We show here that certain areas seem to be more susceptible to hypoxic stress than others, including the hippocampus and substantia nigra. Areas more sensitive to oxidative stress are less clear, but may preliminarily include midbrain and thalamus. We have also developed a technique to stimulate all areas of the brain simultaneously with glutamate. By imaging the turnover of endogenous ($FADH_2$ to FAD^{2+}) we can fit rates of consumption and regeneration of FAD^{2+} in multiple areas of the brain simultaneously.
Ultimately, for all of these methods, we extract quantitative parameters of redox changes in response to activation, hypoxia or oxidative stress and then display the values of these parameters as a heat map image overlaid on an anatomical image of the brain, such as a coronal section. These images will provide a useful way of understanding, visually, complex parameters of brain metabolism. The quantitative nature of these extracted parameters allows them to be tested statistically. We show which parameters are most altered in aging and therefore which would be most useful in detecting the potential protective effects of a variety of interventions , such as exercise in the form of free wheel running, which may preserve brain health. We also report several other indicators of internal and external health including a calculation of metabolic efficiency in whole animals from the CLAMS system, mDNA mutation load with deep sequencing and hearing loss as assessed by auditory brainstem responses.

Disclosures: **K. Stebbings:** None. **K. Murphy:** None. **K. Zwonitzer:** None. **D. Llano:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.22/X21

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: The impact of cofilin1 on mitochondrial dynamics and function in neuronal HT22 cells

Authors: *L. HOFFMANN[1], K. REHKLAU[2], J. GROHM[1], M. RUST[2], C. CULMSEE[1]
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Abstract: Mitochondria are dynamic organelles which undergo permanent fission and fusion to maintain their functions in energy metabolism, calcium homeostasis and regulation of reactive oxygen species (ROS). Genetic defects affecting mitochondrial fission and fusion mediate Charcot-Marie-Tooth neuropathy, and impaired mitochondrial dynamics were also associated with age-related neurological disorders, such as Parkinson's and Alzheimer's disease [1, 2]. Enhanced oxidative stress is considered as a major consequence of mitochondrial dysfunction, and the resulting oxidative stress is also regarded as a major trigger for neuronal dysfunction and cell death in the ageing brain and in multiple neurodegenerative disorders. How oxidative stress mediates neuronal dysfunction and whether the associated mechanisms are accessible for therapeutic intervention strategies is not clarified. Here, we investigated the role of cofilin1, a key regulator of actin and, thereby, mitochondrial dynamics in models of detrimental oxidative stress induced by erastin or glutamate, which induce cell death through increased mitochondrial ROS production and loss of mitochondrial membrane potential. Cofilin1 knockdown was achieved in neuronal HT22 cells by siRNA. Depletion of cofilin1 resulted in increased fission of the mitochondria, without affecting its function in standard culture conditions. Further, we found evidence that cells with fragmented mitochondria upon cofilin1 depletion showed increased cellular resistance against oxidative stress and cell death in paradigms of glutamate and erastin toxicity. Additionally, these cells preserved an intact mitochondrial membrane potential, unaltered ATP production and decreased mitochondrial ROS level despite glutamate or erastin challenges, indicating that cofilin1 knockdown affected mitochondrial resilience against oxidative stress. In contrast, cofilin1 silencing by siRNA could not prevent lipid peroxidation, supporting that cofilin1 knockout mediated effects at the level of mitochondria and did not interfere with upstream mechanisms of glutamate or erastin toxicity. Our findings suggest an important role of actin dynamics regulating mitochondrial fission and homeostasis in paradigms of oxidative stress. In contrast to pathological mitochondrial fragmentation, actin-regulated mitochondrial fission was not associated with impaired mitochondrial function, but may rather

attenuate ROS-induced mitochondrial damage and associated cell death pathways, thereby providing new therapeutic targets for neurodegenerative diseases.
1. Chen H et al. *Human Molecular Genetics* **2009**
2. Nunnari J et al. *Cell* **2012**

Disclosures: L. Hoffmann: None. **K. Rehklau:** None. **J. Grohm:** None. **M. Rust:** None. **C. Culmsee:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.23/X22

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Induced pluripotent stem cell derived excitatory neurons as a neuropsychologic model of MELAS disease

Authors: T. KLEIN GUNNEWIEK[1], D. CASSIMAN[3], E. MORAVA KOZICZ[5,4], N. NADIF KASRI[2], *T. L. KOZICZ[1,5]
[1]Anat., [2]Human Genet., Radboud Univ. Nijmegen Med. Ctr., Nijmegen, Netherlands; [3]Hepatology, [4]Pediatrics, Uz Leuven, Leuven, Belgium; [5]Pediatrics, Hayward Genet. Ctr., Tulane Univ., New Orleans, LA

Abstract: Most individuals diagnosed with the common mitochondrial phenotype of MELAS carry the pathogenic variant 3243A>G in their mitochondrial DNA (mtDNA). Patients show a broad range of symptoms, involving mainly the skeletal muscle and the central nervous system. The mutation being present in the maternally inherited mtDNA, makes generating a knockdown/knockout animal models problematic. In order to increase our understanding on the neuropathobiology of mt.3243A>G we created human cortical neurons (iNeurons), derived from inducible pluripotent stem cells (IPSCs) and studied the impact of mt.3243A>G on mitochondrial- and neuronal (including synaptic) function. Patient-derived fibroblasts were reprogrammed to IPSCs, which were tested for heteroplasmy by sanger sequencing; three clones from the same patient, with different heteroplasmy levels (0%, 72%, and 83%) were expanded. These IPSC's were differentiated into excitatory iNeurons by lentiviral rtta- and Neurogenin 2 (Ngn2) expression. Here we report on the characterization of the iNeurons both at the single-cell and neuronal network level. We also describe whole-cell patch clamp recordings assessing spontaneous excitatory post-synaptic currents (sEPSC's), as well as intrinsic properties, combined with Mitotracker, MAP2- and Synapsin immunocytochemical staining. Additionally, we report on multi-electrode arrays (MEA's) used to study the effects of the 3245G>G mutation on the network activity of the iNeurons. Our study illustrates the relevance of our patient-specific in vitro neurophysiologic model of mitochondrial involvement, which will enhance our

understanding of the role of mitochondrial dysfunctions in neurological manifestations of MELAS disease.

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Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 671.24/X23

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Minor ginsenosides-induced apoptosis of neuroblastoma through loss of MMP and activation of caspase proteins

Authors: J. OH[1], J.-W. LEE[2], *S. CHUN[1,3]
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Abstract: Ginseng has already been proved to exert potential benefits on antitumor activity via its antioxidant properties from other cancer cell lines. In this study, we investigated the potential pharmacological activity of several minor ginsenosides in neuroblastoma cell lines. Among all tested ginsenoside compounds, four minor ginsenosides had strong cytotoxicity and became more effective agents to display the protective effects. As a result, these compounds were significantly increased the apoptosis rate in dose dependent manner which was accompanied by mitochondrial membrane potential (MMP, $\Delta\Psi m$) loss. We found that the expression levels of cleaved caspase 3, cleaved PARP, PUMA and Noxa were upregulated, whereas the expression levels of survivin, Bcl-2, Bcl-xL, MMP-2, MMP-9 protein were down-regulated by treatment of minor ginsenosides. These results suggest that four minor ginsenosides might be promising compounds to have therapeutic effect on neuroblastoma cell lines.

Disclosures: J. Oh: None. **J. Lee:** None. **S. Chun:** None.

Poster

671. Mitochondrial Dynamics and Function in Neurodegenerative Diseases

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Program#/Poster#: 671.25/X24

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NNF12OC0002293

Title: Activation of AMPK affects metabolism of amino acids

Authors: C. M. VOSS, J. V. ANDERSEN, *H. S. WAAGEPETERSEN
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Abstract: Astrocytes and neurons rely on continuous supply of energy substrates in order sustain normal brain function. Therefore mechanisms capable of maintaining energy equivalents are required. AMP-activated protein kinase (AMPK) has until now mostly been investigated in the periphery where it has been described as a master metabolic switch. It was shown previously that AMPK is activated by low energy status in peripheral cells and in turn activates catabolic pathways and inhibits anabolic pathways. The amino acids glutamate (glu) and glutamine (gln) are taken up by astrocytes and neurons and may either enter the Krebs cycle or take part in glutamatergic neurotransmission. How AMPK regulates the metabolism of these important amino acids in brain is however, poorly understood. Pharmacological activation of AMPK was accomplished using the AMP-analogue 5-aminoimidazole-4-carboxamide 1-β-D-ribofuranoside (AICAR). To investigate the metabolic impact of AMPK activation in astrocytes and neurons, acutely isolated hippocampal slices from female NMRI mice were prepared. Slices were incubated in aCSF containing glucose (5 mM) and ^{13}C-labeled glu (0.5 mM) or gln (1 mM) in absence or presence of AICAR (2 mM). Krebs cycle metabolism of glu and gln was assessed with high-performance liquid chromatography supplemented with gas chromatography-mass spectrometry. Increased uptake of ^{13}C-labeled gln and increased metabolism in the Krebs cycle as a response to AMPK activation was observed. Using ^{13}C-labeled glu we observed the same tendency, however not statistically significant. The entrance of glu and gln into the Krebs cycle has an anaplerotic function, since the breakdown of the substrates to Krebs cycle metabolites replenishes the intermediary metabolite pool. However, the Krebs cycle cannot function as a carbon reservoir and therefore cataplerotic mechanisms allowing glu and gln derived carbons to leave the cycle exist. Cataplerosis may be exerted by the action of malic enzyme (ME), which plays an important role in the complete oxidation of glu and gln. Pyruvate recycling is a way for the cells to oxidize amino acids completely, where pyruvate formed in the reaction catalyzed by ME reenters the Krebs cycle via pyruvate dehydrogenase. Increased pyruvate recycling was observed upon AMPK activation when ^{13}C-labeled glu and gln were provided as substrates. These results show that amino acid metabolism in the brain is affected by AMPK activation. Astrocytes and neurons seem to increase their uptake and oxidation of glu and gln thereby maximizing their energetic outcome from these substrates when AMPK is activated and may have consequences for glutamatergic neurotransmission.

Disclosures: C.M. Voss: None. **J.V. Andersen:** None. **H.S. Waagepetersen:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.01/X25

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH intramural grant

Title: calcium dyshomeostasis mediates neural developmental abnormalities in SOD2 deficient cortical neurons

Authors: *A. CHENG[1], Q. ZHAO[2], D. LU[2], M. P. MATTSON[2]
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Abstract: Superoxide dismutases (SODs), including cytosolic and extracellular SODs (SOD1 and SOD3) and mitochondrial SOD (SOD2), are major antioxidant defense enzymes. Germline deletion of SOD2 results neonatal lethality. However, the function of SOD2 in brain development is unknown. We found that brain growth is markedly stunted in $SOD^{-/-}$ mice during the second half of embryonic development. Primary cortical neurons in cultures established from embryonic day 15 $SOD2^{+/+}$ and $SOD2^{-/-}$ mice appear similar during the first 24 hours in culture. During the ensuing two days in culture $SOD2^{-/-}$ neurons in ambient oxygen levels (20%), but not in a reduced oxygen level (3 %), exhibit a profound reduction of neurite outgrowth and subsequently die such that less than 10% of the $SOD2^{-/-}$ neurons remain alive at culture day 5. The mitochondria in $SOD2^{-/-}$ neurons become fragmented and accumulate in cell body well prior to cell death. The structural abnormalities of the mitochondria are associated with reduced levels and phosphorylation (S637) of dynamin related protein 1 (Drp1), a major mitochondrial fission regulating protein, whereas mitochondrial fusion regulating proteins (OPA1 and MFN2) were relatively unaffected. The latter mitochondrial alterations coincide with impaired mitochondrial calcium buffering capacity and an elevation of cytosolic calcium levels. Treatment of $SOD2^{-/-}$ neurons with the Ca^{2+} chelator BAPTA-AM significantly rescues the expression level and phosphorylation of Drp1, as well as neurite outgrowth and cell survival. Collectively, these findings reveal critical roles for SOD2 in maintaining calcium homeostasis in newly generated embryonic cerebral cortical neurons, which is essential for mitochondrial function, neurite outgrowth and cell survival. This research was supported by the Intramural Research Program of the National Institute on Aging.

Disclosures: **A. Cheng:** None. **Q. Zhao:** None. **D. Lu:** None. **M.P. Mattson:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.02/X26

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Grant from Ministry of the Environment

KAKENHI from MEXT of Japan

Title: The molecular mechanism of methylmercury-induced neural degeneration in rat dorsal root ganglion

Authors: *Y. SHINODA[1], S. TATSUMI[1], S. EHARA[1], T. AMEMIYA[1], T. TAKAHASHI[1], Y. SASAKI[2], E. YOSHIDA[2], Y. FUJIWARA[1], T. KAJI[2]
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Abstract: Methylmercury is known as a causal substrate of Minamata disease which is a neurological syndrome, and their symptoms include ataxia, numbness, loss of peripheral vision and damage to hearing and speech. The onset mechanism of Minamata disease, which shows neural degeneration in the specific region including central and peripheral nervous system, has been mainly investigated in the central nervous system; however, the mechanism of neural degeneration in the peripheral nervous system is largely unknown. In the present study, we investigated the molecular mechanism of neural degeneration in the peripheral nervous system using dorsal root ganglion (DRG). Methylmercury chloride solution (2.0 mg/ml) was administrated transgastrically to 9 weeks old Wistar rats at a daily dosage of 6.7 mg/kg/day. The administration cycle, 5 days administration and subsequent 2 days non-administration was used. For immunohistochemistry, the animals were deeply anesthetized by carbon dioxide at 7 or 14 days after first methylmercury administration, and perfused transcardially with PBS followed by 4% PFA. DRG, sensory and motor nerve fibers were prepared from lumber cord (L1-5). For DNA microarray assay, perfusion step was excluded. DRG and nerve fibers were immunostained by neuronal markers (neurofilament, NeuN), myelin marker (MBP), the markers of neuronal subtype in DRG (LDBP, PLXNC1, TrkA, TH). DRG and nerve fibers were unchanged in 7 days sample, however, large number of DRG neurons were degenerated and sensory nerve fiber were disrupted in 14 days sample. Next we prepared non-fixed L1-5 DRG sample from 7 and 14 days after first methylmercury administration for DNA microarray assay. The 1401 and 14858 genes were altered in 7 and 14 days sample compared to control, respectively. The altered genes especially in 7 days were analyzed by The Database for Annotation, Visualization and Integrated Discovery (DAVID) and some key pathways were picked up from the database. Further

investigation is required to clarify the mechanism of neural degeneration in DRG induced by methylmercury and we will show the proceedings at the meeting.

Disclosures: **Y. Shinoda:** None. **S. Tatsumi:** None. **S. Ehara:** None. **T. Amemiya:** None. **T. Takahashi:** None. **Y. Sasaki:** None. **E. Yoshida:** None. **Y. Fujiwara:** None. **T. Kaji:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.03/X27

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: VA Merit Award # I01BX002468-01 to Alpaslan Dedeoglu

Title: Novel mouse model of GWI optimized for the study of the cholinergic system

Authors: *I. CARRERAS[1], N. AYTAN[2], T. MELLOTT[2], L. CRABTREE[3], B. JENKINS[4], J. K. BLUSZTAJN[2], A. DEDEOGLU[1]
[1]VA Boston Healthcare Syst., Boston, MA; [2]Boston Univ. Sch. of Med., Boston, MA; [3]Exeter Univ., Exeter, United Kingdom; [4]MGH-East, Boston, MA

Abstract: The etiology and pathophysiology of Gulf War Illness (GWI) is poorly understood and treatments are lacking. Three drugs used in the Gulf war have been consistently identified as risk factors for the GWI: pyridostigmine bromide (PB), *N*, *N*-diethyl-*m*-toluamide (DEET), and permethrin (PET). These drugs target the nervous system and, via the inhibition of acetylcholine esterase (AChE), the cholinergic system. Although these drugs are considered safe at the doses prescribed, it has been hypothesized that their combination and the stress encountered during the Gulf war deployment may have contributed collectively and synergistically to generate the GWI. It is a priority to design treatments that could reverse the nervous system and the cholinergic defects caused by exposure to these toxins. Here we report a new mouse model of GWI optimized for the study of the cholinergic system. This GWI model is founded on a previously validated one based on the combined exposure to low and relevant doses of PB (1.3 mg/kg/day), DEET (40 mg/kg/day) and PET (0.13 mg/kg/day) and mild restraint stress. The novelty of the model resides on the use of the $ChAT^{BAC}$-eGFP mouse line that express the green fluorescent protein (GFP) exclusively in cholinergic cells allowing to visualize all cholinergic elements of the peripheral and central nervous system. Three months after exposure, mice exposed to the chemicals and stress exhibited memory impairments and increased anxiety compared to control mice that received vehicle only and no stress. Changes in behavior were accompanied with changes on the level of choline acetyltransferase and GFP in the septum. In the hippocampus we found that exposure affected microglial activation, neurogenesis and the neurotrophin BDNF/TrkB and NGF systems. By in vitro magnetic resonance spectroscopy we found

decreased levels of N-acetyl aspartate and GABA in the hippocampus of exposed mice. Experiments were performed in both male and female mice and we report sex differences that will need further investigation. These results support the cholinesterase-inhibiting drug hypothesis of GWI and offer a new animal model that is advantageous in evaluating the effects of cholinesterase inhibiting drugs on the central and peripheral cholinergic systems and provide a model that could expedite the development of treatments for veterans suffering from GWI.

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Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

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Program#/Poster#: 672.04/X28

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Academia Sinica, Taiwan, CDA-106-L01

Title: Investigation the role of TDP-43 oligomers in neurodegenerative diseases

Authors: *T.-Y. WENG, Y.-S. FANG, Y.-R. CHEN
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Abstract: The TAR DNA binding protein 43 (TDP-43) resides mainly in nucleus and plays important roles in the neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTLD). These neuropathology are characterized by deposition of TDP-43-positive cytoplasmic inclusions. In our previous research, we found that the recombinant full-length TDP-43 can form stable oligomers that are neurotoxic *in vitro* and *in vivo*. Such oligomers are also detected in brains of transgenic TDP-43 mice and FTLD-TDP patients using our specific antibody (TDP-O) against TDP-43 oligomers. We next employ our recombinant TDP-43 and TDP-O as the model to investigate the effect of oligomers may involve. Our preliminary data show that the refolded TDP-43 is a TDP-O positive species, and it is more toxic than the TDP-43 S5D or S5A whose TDP-43 exhibits mutation of serine (379,403,404,409,410) to alanine (S5A) for eliminating phosphorylation or mutation of serine (379,403,404,409,410) to aspartic acid (S5D) for simulating hyperphosphorylation. Also, TDP-O antibody shows the neutralization ability by eliminate the cellular toxicity of the refolded TDP-43 in the cell models. Recently, TDP-43 is found to be located in the mitochondria, therefore, we are also interested whether there are other cellular compartments that TDP-43 oligomers may attend. The subcellular localization of endogenous TDP-43 and exogenous TDP-43 oligomers were examined using immunofluorescence. Future directions will be focused on how the TDP-43

oligomers are formed and the cellular localization of these oligomeric TDP-43, and what are the subsequent consequences and its binding partners.

Disclosures: **T. Weng:** None. **Y. Fang:** None. **Y. Chen:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: International Brain Research Organization (IBRO) International Travel Grant Program

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)

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Ciências sem Fronteiras

Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE)

Fundação de Apoio à Pesquisa Científica e Tecnológica do Estado de Santa Catarina (FAPESC)

Title: Adult hippocampal neurogenesis impairment in familial hypercholesterolemia: evidence for a role of the LDL receptor and cholesterol metabolism in adult neural stem cells

Authors: *D. F. ENGEL[1], J. DE OLIVEIRA[3], A. GRZYB[4,5], P. S. BROCARDO[2], G. KEMPERMANN[4,5], A. F. DE BEM[1]
[1]Dept. de Bioquímica, [2]Dept. de Ciências Morfológicas, Univ. Federal de Santa Catarina, Florianopolis, Brazil; [3]Univ. do Extremo Sul Catarinense, Criciúma, Brazil; [4]Deutsches Zentrum für Neurodegenerative Erkrankungen, Dresden, Germany; [5]Ctr. for Regenerative Therapies Dresden, Technische Univ. Dresden, Dresden, Germany

Abstract: Familial hypercholesterolemia (FH) is a disorder of lipoprotein metabolism caused by genetic abnormalities of the low-density lipoprotein (LDL) receptor. The consequent defective catabolism of LDL results in increased plasma cholesterol levels from early age. Recently, clinical and preclinical studies have demonstrated an association between FH, cognitive and mood impairments and neurodegeneration. Since adult hippocampal neurogenesis is implicated in mood and cognition regulation, we hypothesized that the well described cognitive impairments in $LDLr^{-/-}$ mice, a widely used rodent model of FH, may be related to impairment in hippocampal region-dependent behaviors and reduced neurogenesis. Additionally, to dissociate the effects of hypercholesterolemia and of the LDLr absence, we proceeded LDLr gene

knockdown and isolated LDL treatment in adult dentate gyrus (DG) neural stem cells (aNSCs) in vitro. The DG-dependent metric change behavioral test revealed that the $LDLr^{-/-}$ mice presented impairment in DG-dependent cognitive task, compared to C57BL/6 controls. This was corroborated by a reduction in DG cell proliferation and neurogenesis, as assessed 24 h and 28 days following BrdU injections, respectively. Analysis of aNSCs primary cultures, isolated from the DG of adult C57BL/6 mice, demonstrated that the gene expression of enzymes involved in cholesterol synthesis (HMG-CoA reductase and squalene synthase) and of the LDLr peaks during the proliferation stage of the neurogenic process. On the other hand, the gene expression of LRP1, cholesterol 24-hydroxylase, and sterol 27-hydroxylase is up-regulated during the differentiation stage. In agreement with the observations from the $LDLr^{-/-}$ mice, exposure to both human LDL as well as silencing of the LDLr (LDLr siRNA) reduced cell proliferation and/or neuronal differentiation of aNSCs monolayers. LDL treatment was also associated with an increase in the number of lipid droplets and a down-regulation of mRNA levels of the LDLr and enzymes involved in cholesterol synthesis, whereas LDLr siRNA also reduced LRP1 gene expression. The transcriptome differential expression analysis revealed, mainly, that LDL down-regulated cholesterol metabolism processes. Overall, these data indicated a DG-dependent impairment in spatial processing associated to decreased neurogenesis in an animal model of FH. Furthermore, according to our in vitro study both the high cholesterol levels and the LDLr absence might have a role in this outcome. Those results help to underline the function of the LDL receptor and cholesterol metabolism in adult neural stem cells proliferation and differentiation.

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Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.06/X30

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS KAKENHI 16J05812

KANAE Foundation for the Promotion of Medical Science

The Nakabayashi Trust For ALS Research

Title: A novel ALS and FTD model mouse expressing cytoplasmic mutant FUS leads neurodegeneration via synaptic disruption

Authors: *G. SHIIHASHI[1], D. ITO[1], I. ARAI[2], Y. KOBAYASHI[4], K. HAYASHI[3], S. OTSUKA[2], K. NAKAJIMA[3], M. YUZAKI[2], S. ITOHARA[4], N. SUZUKI[1]
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Abstract: Cytoplasmic FUS aggregate is one of the pathological hallmarks in ALS (amyotrophic lateral sclerosis) and FTD (frontotemporal dementia) brain tissue. A major question is whether neurodegeneration is caused by a toxic gain-of-function of cytoplasmic FUS aggregate or a loss of normal FUS function in the nucleus. Therefore, we generated transgenic (tg) mouse line overexpressing exogenous FUS with nuclear localization signal deletion (ΔNLS-FUS tg) related with juvenile ALS with cognitive dysfunction under the control of a neuron specific-promotor Thy-1. ΔNLS-FUS was expressed in the frontal cortex and hippocampus and led age-dependent neuronal loss. ΔNLS-FUS was localized in the cytoplasm while the endogenous FUS did not change in the expression level, nuclear distribution and function for RNA regulation, indicating no loss-of-function of endogenous FUS in ΔNLS-FUS tg mice. ΔNLS-FUS tg mice showed ALS and FTD phenotypes such as progressive motor deficits, hyperactivity, abnormal social interaction, and memory deficit. Golgi staining and immunohistochemistry of synaptic marker revealed decreased dendritic spine and synaptic density in the frontal cortex and hippocampus of ΔNLS-FUS tg mice before neuronal loss. Whole-cell patch-clamp recording from the frontal cortex also showed decreased excitatory synaptic inputs in ΔNLS-FUS tg mice. These results indicate synaptic deficits in ΔNLS-FUS tg mice. ΔNLS-FUS tg mice showed cytoplasmic FUS aggregates positive for ubiquitin and p62. The signal of FISH (fluorescence in situ hybridization) for poly-A-tails of mRNA was colocalized with the cytoplasmic FUS aggregate while the total mRNA levels were decreased at the dendrites of primary culture neurons expressing ΔNLS-FUS. Puromycin labels the newly synthesized proteins, and its intensity was decreased at the dendrites of the cultured neurons expressing ΔNLS-FUS. Collectively, toxic gain-of-function of cytoplasmic FUS is sufficient to lead ALS and FTD phenotypes. Moreover, cytoplasmic FUS aggregate traps the mRNA and impairs its dendritic transport and translation, which leads neurodegeneration via synaptic disruption.

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Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.07/X31

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: The effect of CDNF in the Quinolinic acid toxin model of Huntington`s disease

Authors: *P. STEPANOVA[1], R. K. TUOMINEN[2], D. LINDHOLM[3], M. H. VOUTILAINEN[1]
[1]Inst. of Biotech., [2]Div. of Pharmacol. and Pharmacotherapy, [3]Inst. of Biomedicine, Univ. of Helsinki, Helsinki, Finland

Abstract: Huntington`s disease (HD) is an autosomal dominantly inherited progressive neurodegenerative disorder characterized by motor and non-motor symptoms. Neuropathology of HD is described mostly by degeneration of striatal neurons. Protein folding stress at the ER may contribute to HD-related neurodegeneration. The actual causes of ER stress in HD are poorly understood. Currently, no effective treatment for HD is yet available. The clinical trials of drugs that were used in HD mouse models have failed to delay progression of disease in HD patients. Neurotrophic factors (NTFs) protect and repair injured neurons. It has been shown that several NTFs improve the morphological differentiation and increase the survival ability of striatal neurons *in vitro*. Furthermore, many NTFs were applied in the toxin and genetic models of HD. We have discovered a protein and named it Cerebral Dopamine Neurotrophic Factor (CDNF). CDNF is a secreted protein that is a member of a novel conserved NTFs family, protecting and repairing mammalian dopaminergic neurons *in vivo*. CDNF may regulate ER stress and UPR intracellularly, secreting from the cells to extracellular space during ER-stress. We have shown the therapeutic potential of CDNF in rodent and non-human primates models of PD and showed that CDNF is a potent molecule to protect DA neurons and more importantly restore their function. Importantly, CDNF is a stable protein, which diffuses in brain tissue better than any other neurotrophic factor. Our present results strongly suggest that CDNF regulates endoplasmic reticulum (ER) stress and unfolded protein response (UPR). Moreover, CDNF rescues the only ER-stressed or degenerating neurons and does not influence naïve neurons.
This report represents the first positive neuroprotective effects of a single CDNF administration in QA (Quinolinic acid) rat model of HD. Wistar male rats were received a single unilateral intrastriatal QA-injection (225nmol) and in two weeks after lesion CDNF (10 µg) or vehicle were injected into the same site. Motor coordination and muscle strength were improved in the CDNF-treated group. CDNF significantly increased the number of NeuN-positive neurons in the striatum in comparison with control group. CDNF has significantly postponed the appearance of clinical symptoms in a rat model of HD. Therefore, it seems that CDNF is a potential new drug candidate for treating motor, which is related to Huntington`s diseases.

Disclosures: P. Stepanova: None. **R.K. Tuominen:** None. **D. Lindholm:** None. **M.H. Voutilainen:** None.

Poster

672. Mechanisms of Neurotoxicity

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Instituto de Salud Carlos iii, Miguel Servet fellowship CP12- 03217

Centro de Investigacion Biomedica en Red, Enfermedades Neurodegenerativas (CIBERNED)

Marcelo Botín Foundation

BBVA Foundation

Title: Transcriptomic changes in parvalbumin positive interneurons expressing Cre recombinase

Authors: *X. D'ANGLEMONT DE TASSIGNY, D. ENTERRIA-MORALES, I. LOPEZ-LOPEZ, J. LOPEZ-BARNEO
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Abstract: The use of Cre-lox technology has considerably improved our knowledge in neurobiology. Expressing the bacteriophage-derived, site-specific Cre recombinase in neural cell subsets, allows the conditional deletion, induction or detection of target genes. However, Cre-driver cells may undergo undesired stress that could modify their physiological and metabolic function, and therefore affect the final outcome of a given experiment. In this study, we sought at investigating the transcriptional responses caused by the presence of an active Cre recombinase in the GABAergic interneuron subgroup expressing the Ca^{2+} buffer parvalbumin (PV). For this, we used two reporter mice expressing the red fluorophore tdTomato to capture the PV cells by fluorescence-activated cell sorting (FACS): i) a constitutive *tdTomato* gene inserted in the *Pvalb* locus, and ii) a *PV-Cre-tdTomato* model in which fluorescent cells are Cre-positive. We compared by microarray analysis the transcriptional differences in PV neurons expressing Cre (PV^{Cre}), or not (PV^{wt}), in two anatomically and functionally distinct brain regions: the motor cortex and the dorsal striatum.
Of the 26336 coding and complex genes analyzed, < 4% and < 13% were up- and down-regulated respectively in both PV^{Cre} cortex and striatum. Cortical and striatal PV neurons exhibited a coordinated response to Cre, manifested by a strong up-regulation of genes related to inflammation. This was accompanied by a pronounced decrease in the mRNA expression of ion channels and membrane receptors to GABA, glutamate, serotonin and acetylcholine. These changes differed between cortical and striatal PV neurons as their network, input and function are somewhat different. Gene ontology enrichment analysis also indicated high perturbation of important pathways, such as proteasome degradation, FoxO signaling, HIF-signaling or PI3K-Akt. We have confirmed the microarray differences of selected genes by quantitative RT-PCR, and compared the gene expression in PV neurons versus whole-brain region. Finally, we evaluated the differences observed at the mRNA level of selected proteins (IL1alpha) by ELISA, immunohistochemistry or western blot.
In summary, we provide here a comprehensive transcriptomic analysis showing the adverse effects of Cre expression by PV interneurons, which develop an important inflammation-like response and potential phenotypic changes at the cellular and system levels.

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Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01NS064934- 07

Title: The role of infiltrating myeloid cells in alpha-synuclein neurotoxicity

Authors: *T. N. MALTBIE[1], A. B. WEST[2], A. HARMS[1]
[1]Neurol., Univ. of Alabama At Birmingham, Birmingham, AL; [2]Neurol., UAB, Birmingham, AL

Abstract: Parkinson disease (PD) is a common neurodegenerative movement disorder and results in the loss of dopaminergic neurons in the substantia nigra pars compacta. PD is diagnosed clinically by motor symptoms responsive to dopamine replacement therapies. Pathologically, PD is diagnosed by proteinaceous aggregates called Lewy bodies and neurites in the brain, which consist mainly of the PD-linked protein α-synuclein (α-syn). Analysis of post-mortem tissue in PD demonstrates the accumulation of CD4-postive immune cells from the periphery that infiltrate into susceptible brain tissue. PET-neuroimaging using TSPO ligands shows that inflammation occurs early in PD and does not rescind through the course of disease. However, the contribution of peripherally-derived immune cells in the brain and their impact on neurodegeneration in PD has been difficult to understand. Here, we examine neuroinflammation in the rodent brain after the formation of α-syn inclusions in neurons caused by intra-cranial injections of α-syn fibrils. We find evidence for peripheral immune cell invasion that occurs prior to neurodegeneration. *Ex vivo*, we find that macrophages readily internalize and degrade α-syn fibrils, and in the process, elicit pro-inflammatory responses that may be damaging to nearby neurons. Through correlational observations *in vivo* and mixed immune-cell and primary neuronal cultures *in vitro*, we hope to establish how different inflammatory responses may influence neurodegeneration and the spread of α-syn pathology through the brain.

Disclosures: **T.N. Maltbie:** None. **A.B. West:** None. **A. Harms:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.10/Y1

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Effects of neonatal sevoflurane exposure on the plastic changes in the hippocampus

Authors: Y. SATO, *M. MAEKAWA, S. YAMAGUCHI, Y. HORI
Dokkyo Med. Univ. Sch. Med., Tochigi, Japan

Abstract: Sevoflurane, a widely used anesthetic, affect $GABA_A$ receptor-mediated tonic inhibition. Sevoflurane exposure in an early stage of life induces cognitive dysfunction later in life. However, the mechanisms underlying sevoflurane-induced cognitive impairment are still unclear. In the immature brain, dominant NKCC1 expression leads to high $[Cl^-]i$, which induces a depolarizing GABA response. We observed the behavioral effects of bumetanide, a NKCC1 inhibitor, on sevoflurane-induced cognitive impairment. We also observed the effects of neonatal sevoflurane exposure on functional plastic changes in the hippocampal area CA1.
Neonatal mice (3-5 days old) received an intraperitoneal injection of bumetanide or saline. Just after the injection, the mice were exposed to 2.1% sevoflurane in O_2 for 4 hours. These mice were examined with behavioral tests and electrophysiological recording from 49 days old. The water maze consisted of a 1.2 m diameter circular pool with a hidden platform, and the size of the open-field arena was 40 x 40 x 20 cm. We recorded population spikes (PS) in the hippocampal area CA1 before and after tetanus stimulation (25 Hz, 1 s) of the Schaffer collateral-commissural fibers, and the amplitude ratio (PPR) of the second to the first postsynaptic response after paired pulse stimulation (60 ms interval).
Mice exposed to sevoflurane at P3-5 (P4 mice) showed longer escape latency in the water maze test and spent less time in the target quadrant in the probe test, showing less traveling distance and vertical movement in the novel open-field arena as compared to the control mice. The P4 mice with bumetanide pre-injection showed behaviors similar to those of the control mice. The relative amplitude of PS 30 to 60 minutes after tetanus stimulation in P4 mice was comparable to that in control mice. On the other hand, the relative amplitude of PS 0 to 10 minutes after tetanus stimulation in P4 mice was significantly smaller than that of the control mice. The second postsynaptic response after paired pulse stimulation was facilitated in P4 and control mice, and PPR in P4 mice was significantly less than that of the control mice.
Our results suggest that the effects of neonatal sevoflurane exposure on cognitive behaviors depend on the functional NKCC1 expression, and that neonatal sevoflurane exposure results in the impairment of short-term plasticity in the hippocampal area CA1.

Disclosures: Y. Sato: None. **M. Maekawa:** None. **S. Yamaguchi:** None. **Y. Hori:** None.

Poster

672. Mechanisms of Neurotoxicity

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Grants (2017R1A2B4004289 and 2012M3A9C6049935)

DGIST Convergence Science Center Program (17-BD-04) of the Ministry of Science, ICT and Future Planning of Korea

Title: FAIM2 stability controls the balance of cell death and survival in adult neural stem cells by regulating autophagy

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Abstract: Adult neural stem cells maintain self-renewal capacity and multipotency in the adult brain, thus regulating the output of neurogenesis. Autophagy thought to play a pro-survival role in the cells can kill cells as we have previously shown that autophagic cell death (ACD) is a dominant programmed cell death mode in adult hippocampal neural stem cells subjected to insulin withdrawal in vitro. In postnatal mouse hippocampus, Fas apoptotic inhibitory molecule 2 (FAIM2) gradually increases with age. We found that FAIM2 is expressed in adult hippocampal neural stem cells. Decrease in FAIM2 protein is accompanied by ACD following insulin withdrawal. Prevention of protein synthesis by cyclohexamide showed shorter half-life of FAIM2 in ACD in comparison to that in basal state. Indeed, FAIM2 was post-translationally degraded via autophago-lysosomal pathway. FAIM2 knockdown via siRNA augmented cell death and increased autophagy markers. In summary, our result suggests that FAIM2 protein stability is a critical determinant of neural stem cells' susceptibility to ACD. Our results expand the role of FAIM2, which was previously established as a neuron-specific anti-apoptotic protein, to regulation of autophagy in neural stem cells.

Disclosures: C.J. Hong: None. **H. Woo:** None. **H. Ryu:** None. **B. Yeo:** None. **K. Chung:** None. **S. Ha:** None. **S. Jung:** None. **H. An:** None. **S. Yu:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.12/Y3

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2016R1D1A3B2008194

Title: Neuroprotective effects of sodium orthovanadate against oxidative injury in organotypic hippocampal slice culture

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Abstract: Oxidative injury leads the neuronal cell death due to increased efflux of the excitatory amino acid neurotransmitter glutamate and consequent activation of its receptors. Sodium orthovanadate (Na3VO4, SOV) competitively inhibits the protein tyrosine phosphatases that affected the intracellular proteins phosphorylation. Thus, the present study was conducted to observe the neuroprotective effects of SOV, a protein tyrosine phosphatases inhibitor, on KA-induced neuronal death in OHSC. In addition, we evaluated electrophysiology and behavior study *in vivo* to observe the function of surviving cells by synaptic plasticity in epileptogenesis after SOV treatment in the KA-induced epilepsy model. Neuronal cell death, as assessed by propidium iodide (PI) uptake, was reduced by SOV treatment (24 and 48 h) compared with KA treatment. In the activation of survival signals, the treatment of SOV appears to increase the amount of phospho-Akt and regulate activation of SOD caused by KA-induced injury. In addition, the SOV were resistant to KA-induced behavioral seizure and significantly reduced the epileptiform discharges from the hippocampal neurons. Thus, SOV blocks the acute effects of KA, thereby leading to its neuroprotective effects. These results suggest that SOV may protect hippocampal neurons against oxidative stress and the survived neurons may functional to synaptic plasticity changes (NRF-2016R1D1A3B2008194).

Disclosures: **K. Lee:** None. **U. Kim:** None. **B. Lee:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.13/Y4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Center for Chronic Disorders of Aging

The Adolph & Rose Levis Foundation Laboratory for Alzheimer's Disease Research

Title: Intriguing mixed neuropathology in a case of Lewy body disease

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Abstract: Objective: To determine the extent of neuropathology found in a case of dementia with Lewy bodies. We obtained the brain from a 78 year old deceased male that had been diagnosed with Lewy body disease by exclusion 9 years prior to death. Symptoms exhibited during the course of disease included those typically described in dementia with Lewy bodies with later onset of parkinsonian changes. Lewy body disease is clinically characterized by the following symptoms: dementia, fluctuation, visual hallucinations, and disturbances in attention and executive function. Neuropathological characterization is noted typically by cytoplasmic Lewy body inclusions in cortical and subcortical neurons with alpha-synuclein being the major protein constituent.
Methods: The brain was formalin-fixed and olfactory bulbs, olfactory tracts, optic nerve, optic chiasm, cortical and subcortical regions were prepared for paraffin embedding. Sections from these regions were stained with Periodic Acid Schiff (PAS) with or without diastase digestion as well as immunolabeled with antibodies for a variety of different proteins and infectious agents (Herpes Simplex Viruses 1 and 2, *Chlamydia* species and *Borrelia burgdorferi*). The various proteins included: tau and ptau, GSK3beta, alpha synuclein, TDP43, Abeta 1-42, GFAP, and beta tubulin.
Results: Remarkably, most regions examined demonstrated mixed neuropathology as reflected by immunolabeling with multiple antibodies and PAS staining. Alpha-synuclein presence was notable in both cytoplasmic Lewy bodies and neurites in numerous areas including the amygdala, and temporal cortex. PAS staining of membrane-bound inclusions was very prominent in both olfactory bulbs and tracts as well as in the optic nerve and chiasm. Diastase treatment demonstrated limited digestion of glycogen found in the PAS-positive inclusions. Limited labeling was also observed for Herpes and *Chlamydia* specifically in olfactory and hippocampal regions.
Conclusions: In this particular case of Lewy body disease, neuropathological inclusions were

prominent consisting of those typically found in this disease such as alpha synuclein, but also Alzheimer's disease and other neurodegenerative processes. Intriguingly, because of the extensive amount of PAS-positive inclusions found throughout the brain, this subject may also have had polyglucosan body disease as a comorbid condition. Immunolabeling for infectious agents was also interesting in this case, although the significance of this labeling is inconclusive.

Disclosures: C.J. Hammond: None. **B.J. Balin:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.14/Y5

Topic: D.10. Multisensory Integration

Title: Operant learning in adult rats is impaired following postnatal GABAa receptor blockade

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Abstract: Autism Spectrum Disorder (ASD) is a neurologic disorder often characterized by repetitive behaviors, impairments in social functioning and muted affect. It has been hypothesized that these behavioral manifestations in ASD may be due to atypical sensory perception brought about by an altered framework of neural computation employed by the brain. Neurotypically, perception of sensory stimuli is used to initiate learning which leads to appropriate execution of specific behaviors. Sensory learning is dependent upon a critical balance of excitatory and inhibitory signaling in the brain. Drawing from evidence that suggests that inhibitory (GABAergic) signaling is impaired in ASD, it is likely that this critical balance is shifted and that individuals with the disorder employ an alternative system of neural computation for sensory perception and thus sensory learning. The present study investigated sensory learning in a potential animal model of ASD by inducing GABAergic deficiencies in rats during a critical period of neural development and subsequently testing sensory-based discrimination learning during adulthood. Male rat pups were injected daily with the GABAa receptor antagonist, bicuculline (3 mg/kg), for two weeks and left undisturbed until young adulthood. At approximately 2 months of age the first phase of operant conditioning began. Responses on the left lever were reinforced following presentations of one visual stimulus whereas responses on the right lever were reinforced following presentation of a second, distinct visual stimulus. In the second phase of testing, the two-lever discrimination paradigm was similar with the exception that a third visual stimulus or an auditory stimulus was presented instead of 2 visual stimuli. Rats with GABAergic deficiencies were unable to make stimulus-response associations when stimuli within a pair were of the same modality (i.e., two visual cues), however they were not impaired in the discrimination task when stimuli were different modalities (i.e., a visual stimulus vs. an

auditory stimulus). These results inform the understanding of how disruptions in GABAergic signaling during development may influence sensory decision making in adulthood. Moreover, because animals with GABAergic deficiencies show impairment in sensory learning in some cases but not in others, it can be concluded that sensory learning is itself a spectrum and can be assisted through certain interventions. Results may be generalizable to some members of the ASD population and underscore the need for more specific learning interventions to aid sensory-based decision-making.

Disclosures: O.J. Surgent: None. **S. Robinson:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

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Program#/Poster#: 672.15/Y6

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AA018779

Samuel C. Johnson for Genomics of Addiction Program

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Mayo Clinic-Karolinska Institutet Collaborative Grant

Title: LPS-mediated kynurenic acid and neurogranin-NFAT signaling decrease attentive and cognitive function in mice

Authors: K. WININGER[1], A. OLIVEROS[2], J. SENS[3], S. CHOI[2], S. K. ERHARDT[4], *D.-S. CHOI[2]
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Abstract: Recent studies implicate neuroinflammation in several neurologic and neuropsychiatric disorders including Alzheimer's and schizophrenia and depression. However, the fundamental role it plays in the development of the symptoms is not well understood. Recent discoveries uncover some of the potentially damaging effects of the inflammatory pathways in the brain. The kynurenine pathway is activated by pro-inflammatory cytokines, and kynurenine as well as its metabolite kynurenic acid (KYNA) is increased in these disorders and has been associated with cognitive decline. KYNA is a known non-competitive N-methyl-D-aspartate

(NMDA) receptor antagonist. Given that dysfunctional glutamate signaling is often a correlate of these disorders it is possible that NMDA receptor signaling contributes to the presentation of symptoms. In this study we induce neuroinflammation in C57Bl/6J mice by 2x injections of lipopolysaccharide (LPS) or vehicle (0.83 mg/kg i.p.) 16 hours apart. At 24 hours, mice were either sacrificed and brains were extracted for tissue analysis via western blot, or they underwent behavior (pre-pulse inhibition, rotarod, and pavlovian conditioning). We demonstrate that inducing neuroimflammation through systemic injections of duel-lipopolysaccharide (LPS) impaired stimulus processing during Pavolovian conditioning. These mice concurrently showed increases of N-Methyl-D-Aspartate receptor (NMDAR) antagonist kynurenic acid (KYNA) as well as an increase of NFκB and post-synaptic calmodulin binding protein neurogranin (Nrgn) phosphorylation in medial prefrontal cortex (mPFC) and ventral hippocampus (vHip). This was accompanied by a decreased phosphorylation of calmodulin kinase II (CAMKII) and nuclear factor of activated T-Cells (NFAT).Our results suggest that neuroinflammation, through activation of the KYNA- NMDA-Nrgn pathway, may be associated with attentional processing and cognitive dysfunction. This may provide a novel avenue of investigation for understanding the effects of NMDAR dysregulation in central nervous system (CNS) disorders.

Disclosures: K. Wininger: None. **A. Oliveros:** None. **J. Sens:** None. **S. Choi:** None. **S.K. Erhardt:** None. **D. Choi:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.16/Y7

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Tau-associated extracellular vesicles from various tauopathies differentially impact tau seeding

Authors: *D.-E. CHUNG[1,3], Y. CARLOMAGNO[1], K. R. JANSEN-WEST[1], L. J. LEWIS-TUFFIN[2], S. L. DEVOS[4], M. YUE[1], Y. CHEN[1], L. M. DAUGHRITY[1], I. K. YAN[2], M. DETURE[1], W.-L. LIN[1], T. C. PATEL[2], B. Y. S. KIM[1,2,3], D. W. DICKSON[1], B. T. HYMAN[4], P. J. MCLEAN[1,3], L. PETRUCELLI[1,3]
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Abstract: The microtubule-associated protein tau becomes abnormally aggregated and hyperphosphorylated in various neurodegenerative diseases, which are collectively referred to as tauopathies. Since tau pathology spreads through anatomically connected neural networks, it has been hypothesized that pathological tau species can be released into the extracellular space and

taken up by neighboring naïve cells to initiate tau seeding and propagation. While exact mechanisms underlying cell-to-cell transmission of pathological tau species still remain elusive, recent evidence has proposed extracellular vesicles (EVs) as one of the potential mechanisms of tau seeding and propagation. In an effort to evaluate the effect of tau-associated EVs (tau-EVs) from different tauopathies on tau seeding in a more sensitive and quantitative manner, we utilized the tau RD P301S FRET biosensor cell line that forms punctae of closely associated tau RD-CFP and tau RD-YFP, resulting in a FRET signal that is indicative of tau seeding activity. We first demonstrated that tau seeding can be induced in this biosensor cell line in a dose-dependent manner following treatment with tau-EVs isolated from brain tissues of a tauopathy mouse model rTg4510, which is in keeping with findings from previous reports. Next, we isolated EV fractions from post-mortem brain tissue samples of Alzheimer's disease (AD) and other tauopathy patients, and found that these EV fractions differentially induced tau seeding *in vitro*. Furthermore, to investigate these observations under physiological conditions, we took advantage of our well-established somatic brain transgenesis technique, injecting a novel AAV2/9-TauFRET2 construct into postnatal day 0 (P0) mouse pups by means of intracerebroventricular (ICV) injection. The whole brain transduction of this construct, followed by the injection of EV fractions isolated from different tauopathies, allows for the quantitative and qualitative analysis of tau seeding activity *in vivo*. Taken together, our data suggest that tau-EVs from various tauopathies can modulate tau seeding in a distinct manner. Future studies aimed at identifying the contents of tau-EVs derived from primary tauopathy brains will further aid the development of tau-EVs as a potential biomarker for AD and associated tauopathies.

Disclosures: **D. Chung:** None. **Y. Carlomagno:** None. **K.R. Jansen-West:** None. **L.J. Lewis-Tuffin:** None. **S.L. DeVos:** None. **M. Yue:** None. **Y. Chen:** None. **L.M. Daughrity:** None. **I.K. Yan:** None. **M. DeTure:** None. **W. Lin:** None. **T.C. Patel:** None. **B.Y.S. Kim:** None. **D.W. Dickson:** None. **B.T. Hyman:** None. **P.J. McLean:** None. **L. Petrucelli:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.17/Y8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: KAKENHI 16K12956

Hamamatsu photonics K.K.

Title: The effect of short-duration of the gamma-wave tACS on concentrations of glutamine and glutamate in the dorsolateral prefrontal cortex: An MRS study

Authors: *K. OMATA[1,2], Y. TAKATA[3], S. ITO[4], Y. OUCHI[2]
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Abstract: Purpose: Transcranial alternating current stimulation (tACS) is a noninvasive brain stimulation method with alternating electrical currents applied through electrode pads on the skull at a specific-frequency. Although transcranial direct current stimulation (tDCS) was reported to alter neurotransmitter concentrations such as GABA and glutamate (Glu) measured by magnetic resonance spectroscopy (MRS), the influence of tACS in the concentrations of these chemical substances still remains unclear. Here, we examined the effect of the gamma-wave tACS by measuring the chemical concentrations in the dorsolateral prefrontal cortex (DLPFC) with MRS. Methods: Twenty-four healthy volunteers participated in the tACS-MRS study. Two MRS measurements were conducted before and after the long-duration gamma-wave tACS, and the short-duration one (like a sham stimulation). The tACS delivered an alternating electrical current of 1mA amplitude of gamma frequency (40 Hz) to the brain via 2 electrodes over the bilateral DLPFC. The electrodes were placed on the F3 and F4 by the 10/20 EEG coordinates. In the real stimulation condition, the current with a ramp-up time of 4 s was applied for 10 min. In the short stimulation condition, the current ramped up over 4 s was applied for 20 s. The MEGA-PRESS sequence was used to measure the concentrations of chemical substances, GABA, Glu, Glx, GSH and NAA. LC-model was applied to the analysis of the concentrations of these substances. Results: There was no significant change in chemical concentrations as for the long gamma-wave tACS application, but a significant interaction effect was found in Glx concentration (repeated-ANOVA, $p < 0.017$). The post-hoc analysis showed a significant difference of the Glx concentration between before and after the short-duration application (*t*-test, $p < 0.026$). Discussion: The results showed that the continuous gamma-wave tACS did not alter the cortical chemical conditions significantly unlike the tDCS. Since the tACS generates the cyclic change of electric potentials over the surface of neocortex, this type of cyclic stimulation might keep the chemical concentrations unchanged within the range of the cyclic change. In addition, the two electrodes were symmetrically placed on the both sides of the brain. Hence, an inter-connection effect between the two hemispheres might cancel out significant changes in the chemical states under the tACS. In contrast, there was a significant change of Glx concentration for the short-duration stimulation, suggesting that the small perturbation would affect the chemical state of Glx rather than a typical long application of tACS.

Disclosures: K. Omata: None. **Y. Takata:** None. **S. Ito:** None. **Y. Ouchi:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: RGC GRF PolyU 151033/15M

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RGC GRF PolyU 251006/14M

Title: Quantitative proteomic analysis of human trabecular meshwork (hTM) in response to Rho-associated protein kinase ROCK inhibitor

Authors: *S. SHAN[1], T. C. LAM[1], W. D. STAMER[2], C. DO[1], C. TO[1]
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Abstract: Objective: The trabecular meshwork (TM) is a tissue located in the irido-corneal angle of the eye. It plays an important role in regulating intraocular pressure (IOP) by controlling resistance to aqueous humor drainage and dysfunction results in ocular hypertension/glaucoma. Currently, lack of specific drugs that targets the TM is a set-back for effective glaucoma treatment. Recently, Rho-associated coiled coil-forming protein kinase (ROCK) inhibitors are under development as candidates for TM-targeting, IOP-lowering anti-glaucoma drugs. To better understand the underlying biological mechanisms of ROCK inhibitors, differential protein expression profiles of human TM (hTM) cells in response to treatment by Y39983, a ROCK inhibitor, is investigated by discovery based label-free SWATH-MS approach applied by using a high-resolution Quadrupole-time-of-flight (QTOF) instrument. **Methods**: Primary hTM cell cultures from normal donors were incubated with and without 1μM Y39983 for 48 hours. Staining for actin was performed by using fluorescein phalloidin. Differentially expressed proteins with and without Y39983 were also identified and quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS) using SWATH^{TM} technologies. **Results**: Immunocytochemistry data showed that the intensity of actin staining and number of stress fibers was reduced following Y399833 treatment. By LC-MS/MS, a total of 3949 non-reductant hTM proteins were identified (at 1% FDR). Under specific criteria (p value ≤ 0.05, fold change ≥ 1.5 folds and not less than 2 peptide matches per protein) in SWATH data analysis, 20 proteins were regulated in Y39983-treated hTM cells. The molecular functions of these proteins, as deduced by PANTHER gene list analysis, were related to binding, structural molecule and catalytic activities. In addition, by using STRING v.10 online platform, PI3K-Akt signaling pathway, focal adhesion and ECM-receptor interaction were grouped. **Conclusions:** The ROCK inhibitor, Y39983 alters hTM intracellular actin architecture. The majority of the protein changes in response to Y39983 is novel, including GUSB which may facilitate the breakdown of

glycosaminoglycan. This study demonstrated an exhaustive picture of protein changes by ROCK inhibitor on hTM cells, enhancing the understanding of its mechanistic actions as well as developing potential clinical application as an anti-glaucoma agent.

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Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.19/Y10

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Company of Biologists Ltd (DMM)

Neurochemistry (ISN-CAEN)

Title: MDMA and nicotine interactions impact neurotransmission, motor coordination and working memory in adolescent male mice

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Abstract: 3, 4-methylenedioxymethylamphetamine (MDMA) and Nicotine in take affect several brain centers that has to do with serotonin, dopamine and glutamate transmissions which are used in motor coordination and cognition. We elucidated the effect of chronic injections of MDMA, nicotine and a combined Nicotine-MDMA treatments on motor-cognitive neural functions. In addition, we evaluated the associations between the observed behavioural and neural structural changes induced by these treatments in BALB/c male mice with these two drugs. Sixty (60) young male BALB/c mice weighing 20.5 - 23.5 g were used for this study. The mice were randomly divided into six (6) groups (NIC, MDMA, NIC/ MDMA, NIC + MDMA, MDMA + NIC and Vehicle) of ten (10) mice each; group 1 (NIC) were given 2.0 mg/Kg (s.c.) of nicotine every day for 4 weeks, group 2 (MDMA) were given 2.0 mg/Kg (s.c.) of MDMA twice a week for 4 weeks, group 3 (NIC/MDMA) were given 2.0 mg/Kg (s.c.) of nicotine every day and 2.0 mg/Kg (s.c.) of MDMA twice a week for 4 weeks, group 4 (NIC+MDMA) were given 2.0 mg/Kg (s.c.) of nicotine every day for the 1st 2 weeks follow by 2.0 mg/Kg (s.c.) of MDMA twice a week for the 2nd 2 weeks while group 5 (MDMA+NIC) were given 2.0 mg/Kg (s.c.) of MDMA twice a week for the 1st 2 weeks follow by 2.0 mg/Kg (s.c.) of nicotine every day for the

2nd 2 weeks. The control (group 6) were given 0.2 mL of normal saline (s.c) throughout the 4 weeks. We observed that MDMA caused a decline in motor function, whereas nicotine improved motor function. There was no significant difference in motor coordination/activities for the combined treatment versus the control. Individual treatment with Nicotine and MDMA compact cognitive function and altered dopaminergic, serotonergic and glial activities in prefrontal cortex and dentate gyrus. Also, a combined Nicotine-MDMA treatment also reduced memory activities when compared with the control. This study reviled that Nicotine, MDMA and Nicotine-MDMA treatments significantly reduced memory function and caused structural changes in prefrontal cortex and hippocampus of mice. This study unveiled that MDMA and nicotine induce gliosis and degeneration of neuronal cells of dopaminergic system.

Disclosures: P.A. Adeniyi: None. **O.M. Ogundele:** None. **P.D. Shallie:** None. **C.C. Lee:** None. **A.K. Adefule:** None. **P.A. Adeniyi:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.20/Y11

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: JZ101 deficiency promotes tau pathology

Authors: *F. GAO, ***F. GAO**, J. YANG, J. ZHANG
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Abstract: Microtubule-associated protein Tau (MAPT), a component of the cellular cytoskeleton responsible for microtubule assembly and neuronal stability, is involved in a wide range of neurodegenerative diseases known as Tau pathologies. Here we identified a novel protein named as JZ101, a mitochondrial out membrane protein with great importance in the maintenance of mitochondrial function. We also found a crucial role of JZ101 in the regulation of tau pathologies. The mouse model of forebrains specific depletion of JZ101 demonstrated substantial neurodegeneration accompanying with Tau hyperphosphorylation. The level of AT180 was specifically increased in the forebrains of JZ101 KO mice. However, the levels of phosphorylated AT8 and total tau showed no significant difference between JZ101 KO mice and WT littermates. In conclusion, our findings demonstrate that JZ101 deficiency promotes Tau hyperphosphorylation, and JZ101 might be involved in the pathogenesis of neurodegenerative diseases such as Alzheimer’s disease and Parkinson disease. Our study would also give a new implication for Tau pathologies.

Disclosures: F. Gao: None. **J. Yang:** None. **J. Zhang:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.21/Y12

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Brain-derived exosomes from dementia with lewy bodies propagate alpha-synuclein pathology

Authors: *J. NGOLAB, I. TRINH, E. ROCKENSTEIN, J. FLORIO, M. TREJO, A. ADAME, E. MASLIAH, R. A. RISSMAN
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Abstract: Proteins implicated in neurodegenerative diseases such as Alzheimer's Disease (AD) and Dementia with Lewy Bodies (DLB) have been identified in bodily fluids encased in extracellular compartments called exosomes. Whether exosomes found in DLB patients can seed aggregation is not clear. In this study, exosomes were successfully harvested through ultracentrifugation from brain tissue from DLB and AD patients as well as non-diseased brain tissue. Exosomes extracted from brains diagnosed with either AD or DLB contained aggregate-prone proteins identified in brain tissue through immunohistochemistry. Furthermore, non-diseased mouse brains injected with brain-derived exosomes from DLB patient exhibited prominent alpha-synuclein (α-syn) aggregation. As assessed through immunofluorescent double labeling, α-syn aggregation was observed in $MAP2^+$, $Rab5^+$ neurons. Using a neuronal cell line, we also determined intracellular α-syn aggregation mediated by exosomes is dependent on recipient cell endocytosis. Together, these data suggest exosomes from DLB patients are sufficient for seeding and propagating α-syn aggregation *in vivo*.

Disclosures: J. Ngolab: None. **I. Trinh:** None. **E. Rockenstein:** None. **J. Florio:** None. **M. Trejo:** None. **A. Adame:** None. **E. Masliah:** None. **R.A. Rissman:** None.

Poster

672. Mechanisms of Neurotoxicity

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Program#/Poster#: 672.22/Y13

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: FWF P26881 to AK

FWF F4414 to NS

Center for Molecular Biosciences Innsbruck

Title: The neuroretina in multiple system atrophy: Morphological implications of Plp-α-Syn mice

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Abstract: Neurodegenerative diseases like Parkinson's disease (PD) and Multiple System Atrophy (MSA) have been shown to exhibit physiological and morphological neuronal abnormalities. These abnormalities can result from exceeding aggregation of α-synuclein (α-SYN), a 140aa presynaptic protein that exerts toxic function in case of dysregulation. Both PD and MSA are associated with a variety of visual symptoms and a potential role of the retina as a biomarker for progression of Parkinson's disease is recently discussed. We therefore aimed at investigating the underlying mechanisms in homozygous transgenic mice overexpressing human α-SYN under the proteolipid protein (PLP)-promoter (PLP-α-SYN) compared to wild type (WT) animals of two different age groups (two months, one year). By performing immunohistochemical analyses on vertical retinal sections we discovered that distinct α-SYN signal occurred in different retinal cell layers of PLP-α-SYN mice, but not in WT mice. This is remarkable as the PLP promotor driving the α-SYN expression in oligodendrocytes was reported to be inactive in the retina. PLP expression stopped at the optic nerve/retina junction, where we observed a colocalization with α-SYN. Notably one cell type distinctly stained in the inner retina appeared to be rod bipolar cells, an assumption confirmed by PKCα co-staining. Quantitative real-time PCR using specific TaqMan® probes will help to verify the specificity for α-SYN immunoreactivity in rod bipolar cells. Interestingly, immunoreactivity for α-SYN was more distinct in peripheral rod bipolar cells than in central ones. Additional immunohistochemical experiments included the investigation of the glial fibrillary acidic protein (GFAP), a marker for activation of Müller glia that can indicate neuroinflammatory processes, and Iba1, a marker for microglial activation. GFAP-positive fibers spanning the peripheral retina were pronounced in aged animals in WT and even more in PLP-α-SYN. This might reflect also the direction of accumulation human α-Syn in rod bipolar cells, which proceeds in the same way. In preliminary experiments Iba1 expression seemed comparable. Due to the known impairments of the dopaminergic system in α-synucleinopathies we investigated also dopaminergic neurons. Although the cell bodies seemed deformed in PLP-α-SYN animals their number was comparable. Tyrosine-hydroxylase-positive processes however appeared to reach into deeper strata of the inner plexiform layer. Our finding clearly implicated an impairment of retinal neurons in the PLP-α-SYN MSA model, which may also underlie visual deficits reported in MSA patients.

Disclosures: **K. Kaehler:** None. **H. Seitter:** None. **A. Sandbichler:** None. **N. Stefanova:** None. **A. Koschak:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.23/Y14

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: BAP 2015-056 HDP

Title: Effects of retigabine on endoplasmic reticulum stress induced by thapsigargin and tunicamycin in PC12 cells; a comparative study

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Abstract: Retigabine (RTG) is an anticonvulsant drug used in the treatment of partial seizures and acts through the activation of M-type current dependent on KCNQ channels. Valporic acid (VPA) enhances GABA B receptor levels and decelerates glutaminergic transmission. Thapsigargin (Tg) is commonly used as an ER (Endoplasmic Reticulum) stress agent conducting calcium depletion by blocking SERCA. Tunicamycin (Tun) blocks N-glycosilation reactions in protein folding process. The aim of this study was to compare effects of RTG and VPA on Ca^{2+} influx and cell death in PC12 cells under ER stress induced by Tg and Tun.
$8x10^4$ cells were seeded per well on poly-L-lysine coated 96-well cell culture plates. The cells were cultured in DMEM supplemented with 5% fetal bovine serum, 5% horse serum and 1% Pen-Strep for three days to obtain confluency. Then the cells were threated with 1% NGF in DMEM for 72 hours to induce differentiation. Following treatment, the media were removed and the cells were incubated with 100 µl 20 mM glucose KRB buffer and 100 µl FLIPR Ca^{2+} assay kit (Molecular Devices) for 2 hours. 25 µM RTG or 10 nM VPA were added and incubated for 20 min prior to measurement of Ca^{2+} influx. Fluorimetric data (n=3) was acquired on the FlexStation3 (Molecular Devices) with an excitation wavelength of 485 nm and an emission wavelength of 525 nm. The FlexStation3 was set to run for 10 min, collecting data at 2.5-second intervals, with stimulation of the cells (1000 nM Tg or 1µg/mL Tun) occurring at 60 s. Cell proliferation (n=4) was measured after 24 hours of ER stress by using WST-1 assay (Roche). One way Anova was used to compare cell viability results.
Tg and Tun treatment decreased cell viability when compared to the control group. Tg dramatically increased cell toxicity and Ca^{2+} influx. Vacoulization and loss of cell adhesion were

observed. RTG and VPA treatment decreased the detrimental effects of Tg and Tun, respectively, on cell viability. Tun enchanced cell toxicity but had no effect on Ca^{2+} influx. Compared to the control group, especially VPA and Tun enhanced cell proliferation when applied together.
The protective effect of VPA against ER stress was known, but the effect of RTG on ER stress is still unclear. According to our results, RTG has protective effects on cell viability and Ca^{2+} influx regulation in ER stress induced by Tg.

Disclosures: S. Karadenizli: None. **D. Sahin:** None. **H. Kenar:** None. **C. Yilmaz Ozdogan:** None. **N. Ates:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

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Program#/Poster#: 672.24/Y15

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01ES024745

Title: Loss of Nlrp3 protects neurons against environmental toxicant exposure *In vitro*

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Abstract: Inflammation has long been associated with age-related neurodegenerative diseases and there is increasing evidence of an environmental component influencing the incidence and progression of brain disorders. In this context, there is a great interest in sterile inflammatory mechanisms triggered by exposure to environmental toxicants, including pesticides, heavy metals, and industrial solvents. The NLRP3 inflammasome complex is an innate immune pro-inflammatory mediator involved in the maturation of pro-inflammatory cytokines that can be activated by non-pathogenic triggers such as oxidative stress and misfolded proteins. NLRP3 has been shown to be upregulated in neurons following cerebral infarction and our laboratory has found evidence of elevated NLRP3 expression in mesencephalic neurons in tissues obtained from Parkinson's disease patients. These data suggest that distressed neurons may operationalize the inflammasomes initiating, or contributing to, the neuroinflammatory state. Our laboratory and others have found activation of the *Nlrp3* inflammasome resulting from exposure to the Parkinson's disease-associated pesticide rotenone and evidence suggesting that abolishing its function may be neuroprotective. Here we screen a panel of environmental neurotoxins to determine if *Nlrp3* is required for neurotoxicity using primary cortical neurons established from

wild type (WT) and *Nlrp3*$^{-/-}$ mice. The effects of *Nlrp3* loss-of-function varied across the different groups of toxicants. *Nlrp3*$^{-/-}$ cultured neurons were resistant to toxicity elicited by high doses of organophosphate and organochloride pesticides including diazinon, chlorpyrifos, and dieldrin as compared with identically treated wild type neurons. The results indicate that inhibition of *Nlrp3* is a rational neuroprotective strategy and suggest that further analysis will identify pathways of interest for understanding the impact of environmental toxicant exposure on the central nervous system.

Disclosures: F. Anderson: None. **A.L. Young:** None. **H.H. Yeh:** None. **M.C. Havrda:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.25/Y16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Brigham Young University, College of Life Sciences, Mentoring Environment Grant

NIH/NIA 1 R21 AG037843; Brigham Young University, School of Family Life, Gerontology Program; Brigham Young University, Dr. Sarah M. McGinty Neuroscience Graduate Student Research Fellowship; Neurodar, LLC; Limitless Worldwide, LLC

Title: Analysis of Tau, A-beta, and Iron stains in the Subiculum of the Hippocampus

Authors: *C. M. COTTAM, A. P. COX, K. BURNINGHAM, S. TUNG, M. STONE, J. BRIDGEWATER, T. KAVAFYAN, K. STEED, E. M. STARK, H. DONG, A. W. TOGA, H. V. VINTERS, J. J. WISCO
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Abstract: Iron, A-beta, and Tau Colocalization in the Subiculum During Braak Stage Progression in Progressive AD and Cardiovascular Disease Pathologies.

Introduction

Alzheimer's Disease (AD) is associated with several pathological protein aggregates in the brain, particularly in the hippocampus. We have demonstrated that excessive non-heme iron deposits co-localizing with amyloid-beta (Aβ) plaques and hyperphosphorylated tau (HP-Tau) are a hallmark of AD pathology. The goal of this project is to investigate the timing of amyloidosis and taopathy with iron dysregulation through Braak stage progression, and with added presence of cerebrovascular disease (CVD). We hypothesized that in the subiculum of the hippocampus, the relationship between neuropathology and iron dysregulation will be similar between both diseases.

Methods
We histologically processed medial temporal lobe biopsies of 35 subjects and analyzed those classified as Braak stage I-III (3 subjects), IV-V (4 subjects) VI (2 subjects), CVD (1 subject), IV-V+CVD (4 subjects), VI+CVD (5 subjects) and control (3 subjects). We used the DAB-enhanced stains for non-heme iron (Perls'), anti-Aβ-42, anti-Tau and anti-CD68 on 6 micron coronal slices, and scanned followed by visualization using a Leica SCN400 and Leica Digital Image Hub environment, respectively. Images were qualitatively analyzed for the presence of each stain in the EC using 15x-25x magnification.
Results
The subiculum exhibited deposition of (Aβ) plaques and HP-Tau with non-heme iron as early as Braak I-III, and throughout stages IV-V and V. This is similar with CVD and the addition of CVD at any of the Braak stages. Control subjects did not exhibit any pathology.
Conclusions
The subiculum is an important gateway of the entorhinal cortex to hippocampus functional anatomy. Iron dysregulation accompanies amyloidosis and tauopathy in the subiculum at all Braak stages, CVD alone, and CVD with AD, indicating that non-heme iron may play an important role in the early as well as late in the neurodegenerative process.

Disclosures: C.M. Cottam: None. **A.P. Cox:** None. **K. Burningham:** None. **S. Tung:** None. **M. Stone:** None. **J. Bridgewater:** None. **T. Kavafyan:** None. **K. Steed:** None. **E.M. Stark:** None. **H. Dong:** None. **A.W. Toga:** None. **H.V. Vinters:** None. **J.J. Wisco:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

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Program#/Poster#: 672.26/Y17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA 1 R21 AG037843

Title: Effects of oxidative insult with rescue diets and T2 signal dropouts in the hippocampus

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Abstract: Introduction:
Alzheimer disease (AD) is a neurodegenerative disease leading to dementia that causes problem with memory, cognition and social behavior. Depositions of iron in the brain have been thought to be an important event in the neurodegenerative process, and are associated with beta-amyloid

plaques and tau proteins in AD brains. Iron can catalyze free radical reactions and contribute to oxidative damage as seen in such disease. Hence, MR imaging of such iron deposition was proposed as a biomarker to evaluate the pathogenesis and progression of AD.
Methods:
T2-weighted turbo-spin echo (TSE) MR images acquired at 1, 3, 6 and 9 months of age of transgenic mice producing higher amount of amyloid beta (APP/PS1) or Tau proteins, and age-matched wild types (WT) were analyzed for signal intensity in a hippocampal ROI (region of interest). Sub-cohorts of mice received an oxidative insult and were rescued with Metformin, clioquinol or zinc, all through ad libitum diet. We used a Litz birdcage coil sized specifically for a mouse to acquire the images on a Siemens Trio. Voxel size was small (0.27 x 0.27 x 0.9mm), which allowed 16 averages to achieve adequate SNR. The TR/TE = 8000/115 ms, and flip angle was 150 deg. Images were visualized and analyzed on the Osirix platform. Mean pixel values of a ROI (Area: 2.001 mm^2, W: 1.694 mm H: 1.504 mm P: 5.0 mm) from hippocampus as a ratio of maximum pixel values of the ipsilateral eye were statistically analyzed using a repeated measures one-way ANOVA.
Results:
Eighteen APP/PS1 mice, 18 Tau, and 18 WT mice were imaged and analyzed separately for the effect of time on mean T2 TSE signal. APP/PS1 [$F(3, 21) = 5.410$, $p=0.006$] and Tau [$F(3, 21) = 11.861$, $p<0.001$], but not WT [$F(3, 21) = 0.705$, $p=0.560$] mice showed a significant signal decline with age in the left hippocampus. Likewise, APP/PS1 [$F(3, 21) = 4.720$, $p=0.011$] and Tau [$F(3, 21) = 8.384$, $p=0.001$], but not WT [$F(3, 21) = 0.493$, $p=0.691$] mice showed a significant signal decline with age in the right hippocampus. There was no effect of oxidative insult or diet rescue on T2 TSE signal.
Conclusions:
Expected accumulation of the pathological proteins beta-amyloid and tau in the hippocampus of the respective APP/PS1 and Tau transgenic mice appeared to result in a measurable T2 signal decay compared with that of WT mice. However, the oxidative stress and rescue treatments didn’t affect the outcome. Future studies include histological and Western blot confirmation.

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Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.27/Y18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Brigham Young University, College of Life Sciences, Mentoring Environment Grant

NIH/NIA 1 R21 AG037843; Brigham Young University, School of Family Life, Gerontology Program; Brigham Young University, Dr. Sarah M. McGinty Neuroscience Graduate Student Research Fellowship; Neurodar, LLC; Limitless Worldwide, LLC

Title: Amyloidosis, tauopathy, and microglial activation in the entorhinal cortex of alzheimer's disease versus frontotemporal dimentia with cerebrovascular disease

Authors: *A. P. COX[1], C. M. COTTAM[1], K. M. BURNINGHAM[1], S. TUNG[2], M. STONE[2], J. BRIDGEWATER[2], T. KAVAFYAN[2], K. STEED[1], M. E. STARK[2], H. DONG[3], A. W. TOGA[3], H. V. VINTERS[2], J. J. WISCO[1,4]
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Abstract: Introduction:
Pathological deposition of amyloid-beta (Aβ) plaques followed by neurofibrillary tangles comprised of hyperphosphorylated tau (HP-Tau) in the hippocampus and entorhinal cortex (EC) is a hallmark of Alzheimer's disease (AD). Our working hypothesis is that non-heme iron co-localizes with the Aβ plaques in early Braak stages, but will associate with HP-Tau tangles in later stages. Changes in co-localization of iron with these proteins in the EC across Braak stages is not well-known. In addition, the activation of microglia in relation to the iron response pathology in the EC is not well-characterized. We hypothesize for this experiment that as Braak stages progress, non-heme iron will co-localize with Aβ initially, then additionally with HP-Tau in the EC, and that this progression is concomitant with activation of microglia. We contrasted this with the pathology of frontotemporal dementia with cerebrovascular disease (FTD+CVD) in the EC.
Methods:
We histologically processed medial temporal lobe biopsies of 35 subjects and analyzed those classified as Braak stage I-III (3 subjects), IV-V (4 subjects), VI (2 subjects), FTD+CVD (2 subjects), and control (3 subjects). We used the DAB-enhanced stains for non-heme iron (Perls'), anti-Aβ-42, anti-Tau and anti-CD68 on 6 micron coronal slices, and scanned followed by visualization using a Leica SCN400 and Leica Digital Image Hub environment, respectively. Images were qualitatively analyzed for the presence of each respective stain in the EC using 15x-25x magnification.
Results:
Aβ and HP-Tau were present in the EC as early as Braak I-III, in addition to co-localized non-heme iron and activated microglia. This spatial relationship is also present in Braak IV-V and VI. FTD+CVD subjects exhibited a similar pattern, but in the absence of Aβ plaques.
Conclusions:
Tauopathy associated with non-heme iron deposition and microglial activation are events that occur early in AD and FTD+CVD pathology, but only AD includes Aβ plaque formation. This indicates that iron dysregulation and inflammatory processes are non-specific for these two different neurodegenerative processes, and corroborates the specificity of the formation of Aβ plaques to AD.

Disclosures: **A.P. Cox:** None. **C.M. Cottam:** None. **K.M. Burningham:** None. **S. Tung:** None. **M. Stone:** None. **J. Bridgewater:** None. **T. Kavafyan:** None. **K. Steed:** None. **M.E. Stark:** None. **H. Dong:** None. **A.W. Toga:** None. **H.V. Vinters:** None. **J.J. Wisco:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.28/Z1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Brigham Young University, College of Life Sciences, Mentoring Environment Grant

NIH/NIA 1 R21 AG037843; Brigham Young University, School of Family Life, Gerontology Program; Brigham Young University, Dr. Sarah M. McGinty Neuroscience Graduate Student Research Fellowship; Neurodar, LLC; Limitless Worldwide, LLC

Title: Comparison of colocalization of non-heme iron with Ab and Tau throughout Braak progression of AD in CA1, subiculum, and entorhinal cortex

Authors: *K. BURNINGHAM[1], A. P. COX[1], C. M. COTTAM[1], S. TUNG[2], M. STONE[2], J. BRIDGEWATER[2], T. KAVAFYAN[2], K. STEED[1], M. E. STARK[2], H. DONG[3], A. W. TOGA[3], H. V. VINTERS[2], J. J. WISCO[4,1,2]
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Abstract: INTRODUCTION
The buildup of amyloid-beta (Aβ) plaques and tau tangles in the brain, particularly in the hippocampus, is a hallmark of Alzheimer's disease (AD). We previously showed that extracellular non-heme iron deposits co-localize with these aggregates. However, the degree to which this co-localization varies according to the separate architectonic hippocampal areas, and according to Braak I-VI progression, is not well documented. To this end, we compared the CA1 and subiculum hippocampal subfields. We hypothesized that iron co-localization with Aβ precedes tau through advancing AD and will be more pronounced in CA1 compared with the subiculum based on the perforant pathway connectivity.
METHODS
We histologically processed medial temporal lobe biopsies of 35 subjects and analyzed those classified as Braak stage I-III (3 subjects), IV-V (4 subjects) VI (2 subjects), and control (3 subjects). We used the DAB-enhanced stains for non-heme iron (Perls'), anti-Aβ-42, and anti-

Tau on 6 micron coronal slices, and scanned followed by visualization using a Leica SCN400 and Leica Digital Image Hub environment, respectively. Images were qualitatively analyzed for the presence of each respective stain in the EC using 15x-25x magnification.
RESULTS
The subiculum, along with the entorhinal cortex, exhibited co-localization of non-heme iron with (Aβ) plaques first, followed by HP-Tau as early as Braak I-III, and throughout stages IV-V and VI. This pattern was similar in CA1, but lagged behind the pathology progression of the subiculum. By stage VI, none-heme iron co-localizes with HP-Tau more than with Aβ. Control subjects did not exhibit any pathology.
CONCLUSIONS
The subiculum is anatomically adjacent to the entorhinal cortex, but follows CA1 in the perforant pathway. The chronological order of Aβ deposition followed by the formation of HP-Tau tangles, and the concomitant none-heme-iron deposition, however, does not appear to follow this pathway. This suggests that the subiculum and entorhinal cortex should be considered together in the progression of AD pathology.

Disclosures: **K. Burningham:** None. **A.P. Cox:** None. **C.M. Cottam:** None. **S. Tung:** None. **M. Stone:** None. **J. Bridgewater:** None. **T. Kavafyan:** None. **K. Steed:** None. **M.E. Stark:** None. **H. Dong:** None. **A.W. Toga:** None. **H.V. Vinters:** None. **J.J. Wisco:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.29/Z2

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIAAA Grant AA020022

Title: The change of cell death signaling in the hippocampus of alcoholic human and rat brain following adolescent intermittent ethanol exposure

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Abstract: We previously found that adolescent intermittent ethanol (AIE) exposure decreased neurogenesis, and increased apoptosis of neuronal cells in the hippocampus. Apoptosis can be induced by activation of death receptors, including DR3, Fas, DR4 and DR5 by their individual ligands. To investigate the impact of AIE exposure on cell death signaling pathway in adult rat and human post-mortem alcoholic brain, the protein expressions of cell death cascade were assessed in the granular cell layer (GCL) of the hippocampus using immunohistochemistry

(IHC). For animal brain study, male Wistar rats were exposed with ethanol (5 g/kg, i.g., 2 days on-2 days off, PND25-54). Animals were sacrificed at P95 for brain sectioning and IHC with active caspase-3, death receptor 3 (DR3/TNFRSF25) and TL1A/TNFSF15, the ligand of cell death receptor. For human brain study, the paraffin sections of human post-mortem hippocampus were obtained from the New South Wales Tissue Resource Center at the University of Sydney in Australia. Markers of cell death signaling pathway were assessed in human hippocampus with IHC. We found that AIE exposure remarkably increased DR3+IR (204% of control, $p<0.01$), TL1A+IR (184%, $p<0.01$) and active caspase-3+IR (138%, $p<0.01$) in the GCL of rat brain. These findings prompted the further investigate of death receptor signaling cascade in the human post-mortem alcoholic brain. Our data have indicated that DR3+IR (267 %, $p<0.05$) and TL1A+IR (364%, $p<0.01$) were significantly increased compared to controls in the human post-mortem alcoholic GCL, respectively. The expression of the two pivotal Death Domain (DD), FADD+ (469%, $p<0.05$, Fas-associated DD), pFADD+ (342%, $p<0.01$) and TRADD+IR (414%, $p<0.05$, TNF receptor-associated DD), were also increased. We found that active caspase-8+IR in the GCL of alcoholic brain was significantly increased (292% of control, $p<0.05$) with active caspase-9 showing a trend increase. The two executioner caspases were also increased, active caspase-3+ (356%, $p<0.05$) and caspase-7+IR (385%, $p<0.05$). The expression of DR3, its ligand and active caspase-3 in alcoholic GCL are consistent increase with ethanol exposure in rat brain following AIE. Fas+IR expression did not show any change, but its ligand, FasL+IR expression was remarkably increased in the Alcoholic GLC. Further NFκB p65+ and IL8+IR expression were significantly increased in the Alcoholic GLC. The these data indicate that human post-mortem alcoholic brain and adult rats following AIE exposure show increased expression of DRs, activated caspases and DR signaling proteins in hippocampus. (Supported by NADIA from NIAAA).

Disclosures: W. Liu: None. **F.T. Crews:** None.

Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.30/Z3

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIDA Intramural Research Program

NCATS Intramural Research Program

Title: Monitoring endoplasmic reticulum calcium and proteostasis in neurons under hypoxic conditions

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Abstract: The pathophysiological mechanisms underlying neuronal death following a stroke occur through the temporal, concerted dysregulation of many cellular processes. ER calcium is important for many cellular functions, such as protein folding, lipid metabolism, and signaling pathways. Disruption of ER calcium homeostasis has been implicated in multiple neurological diseases, including stroke. We used secreted ER calcium-modulated proteins (SERCaMPs) to monitor ER calcium depletion using in vitro and in vivo models of stroke. Using a previously described Gaussia luciferase (GLuc)-SERCaMP in vitro, we demonstrate here that oxygen and glucose deprivation increased ER calcium depletion and decreased cell viability. Additionally, we developed and screened a series of GLuc-based SERCaMP reporters representing ~80 ER resident proteins. The observed changes in reporters indicate a significant departure of proteins from the ER in response to ischemia-induced ER calcium depletion which we have termed “ER exodosis.” This increase in SERCaMP response was attenuated by treatment with the RyR antagonist dantrolene, which also attenuated ER calcium depletion and increased cell viability. Rats injected with AAV vectors expressing GLuc-SERCaMP in the cortex showed evidence of ER calcium depletion following occlusion of the middle cerebral artery. Furthermore, dantrolene treatment reduced the infarct volume in rats. Collectively, our data supports a model in which ischemic injury causes ER calcium depletion and ER exodosis. These effects can be attenuated by stabilizing ER calcium and preventing loss of ER resident proteins.

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Poster

672. Mechanisms of Neurotoxicity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 672.31/Z4

Topic: G.03. Emotion

Support: DARPA Cooperative Agreement Number W911NF-14-2-0045

Title: Striatal brain stimulation improves cognitive flexibility by modulating the human dorsal anterior cingulate

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Abstract: Deep brain stimulation (DBS) is used to treat drug resistant pathologies such as movement disorders, epilepsy, and pain and is being trialed for managing psychiatric disorders. Unlike movement disorders and epilepsy which are characterized by well-defined symptoms, psychiatric disorders have heterogeneous presentations with overlappting functional deficits across disorders. Cognitive rigidity and impaired top-down control are found across anxiety and mood disorders. A DBS paradigm that directly improved cognitive flexibility might effectively treat multiple disorders.Cognitive flexibility includes the ability to rapidly shift attention and behavioral strategies in response to changes in the environment. We assessed flexibility with a Multi-Source Interference Task (MSIT). MSIT requires subjects to identify which of three stimuli (numbers) is different than its neighbors. In Interference (I) trials, the number is out of position and is flanked by valid-target distractors. Patients undergoing invasive monitoring for epilepsy surgery performed the MSIT over several blocks of trials. Short trains of dorsal and ventral striatal stimulation at 130 Hz, 6 mA were delivered during a pseudo-randomized 50% of trials. We found a significant effect ($p<0.01$, multivariate regression) of right dorsal striatal stimulation in improving cognitive flexibility in all 6 patients who received right dorsal striatal stimulation. In 5/6 patients, left dorsal striatal stimulation had a similar effect. On a group level, left dorsal, left ventral and right dorsal had a significant effect on improving cognitive flexibility, while right ventral stimulation did not. We calculated a Spearman's correlation coefficient between the cognitive flexibility state (estimated from reaction time) and High Gamma Power (HGP, 65-200 Hz) in dACC during the first 0.5 seconds after image onset. In 4/6 patients, HGP in left and right dACC channels correlated with behavioral flexibility. These were also the same patients who had a significant improvement in flexibility with stimulation. The two patients that showed a negative correlation between dACC HGP and behavior were unaffected by striatal stimulation. From initial analysis, we conclude that dorsal striatal stimulation improves cognitive flexibility by modulating neural firing (reflected in HGP) in the dACC. This feature can be used to design closed loop stimulation strategies for improving cognitive flexibility in patients with mood and anxiety disorders.

Disclosures: I. Basu: None. **A.C. Paulk:** None. **K. Farnes:** None. **B. Crocker:** None. **M.M. Robertson:** None. **D.D. Dougherty:** 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.; Cyberonics, Medtronic. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Medtronic. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Medtronic. **S.S. Cash:** None. **E.N. Eskandar:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Medtronic, NeuroPace. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cerenova. **A.S. Widge:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Medtronic.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.01/Z5

Topic: C.08.Stroke

Support: R01NS084028

R01 NS078223

Title: Recovery of cortical delta band functional connectivity after focal ischemia

Authors: *Z. P. ROSENTHAL[1], J.-M. LEE[2]
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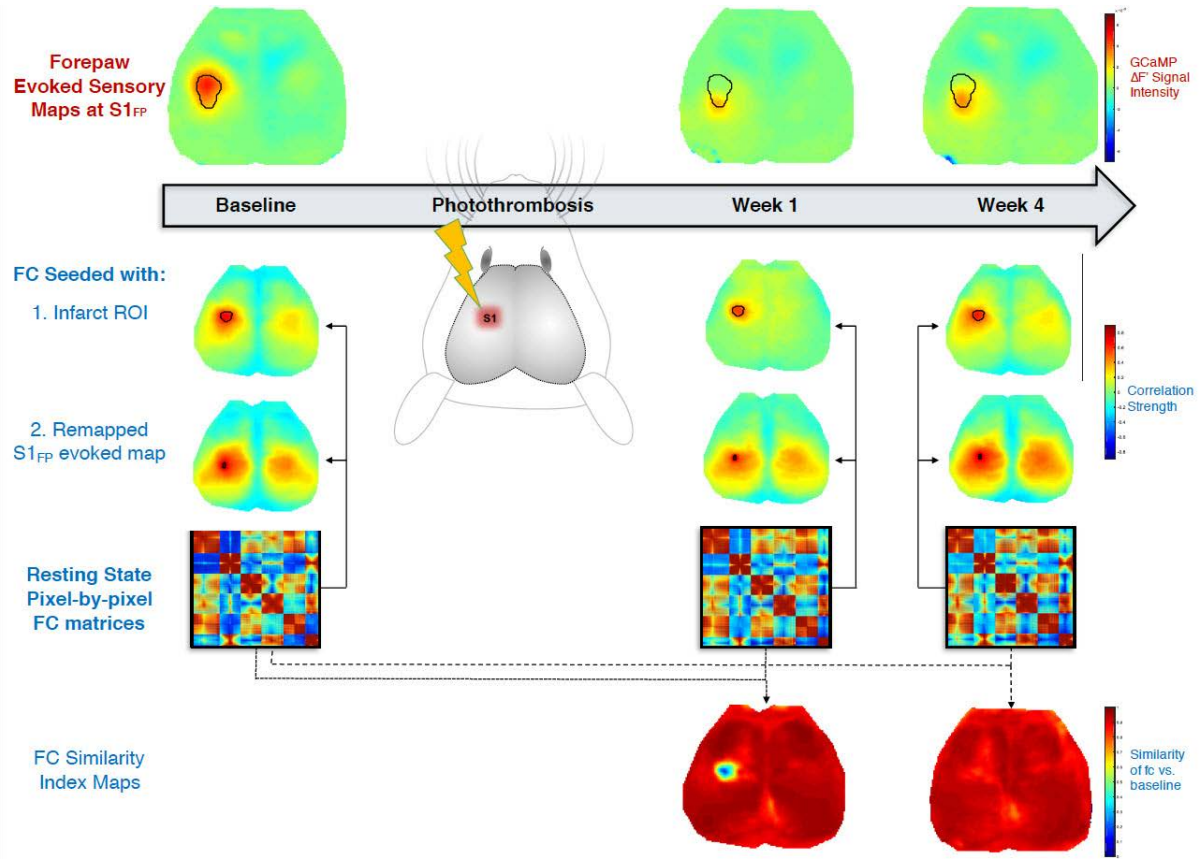
Abstract: Stroke, a leading cause of disability, has a $34 billion economic burden annually. Recovery from stroke, though often limited, is associated with repair of microcircuits in peri-infarct tissue (termed remapping), as well as re-establishing functional connectivity (fc) with larger brain networks. Prior studies have examined these changes in network connectivity using hemodynamic signals (e.g. BOLD fMRI), which are limited to slow activity (<0.5Hz) and may be contaminated by neurovascular uncoupling. In this study, we use a fluorescent calcium-based indicator (GCaMP) to circumvent these shortcomings by directly reporting on neuronal activity, and reveal distinct changes in delta band (0.5-4 Hz) connectivity in a mouse model of stroke. Sixteen male *Thy1*-GCaMP6f transgenic mice underwent photothrombosis of the forepaw sensory cortex ($S1_{FP}$). Cortical neuroimaging was performed serially, before and after photothrombosis. At each time point, we measured awake spontaneous GCaMP activity, as well as evoked responses to forepaw electrical stimulation to track remapping of the $S1_{FP}$ cortex. Resting state activity was analyzed for pixel-by-pixel correlations (fc matrices), maps of fc with key seed regions, and similarity between correlation maps over time. At baseline, we observe focal activation of the left $S1_{FP}$ during right forepaw stimulation; activity at rest shows strong local ipsilateral and homotopic (contralateral) fc. One week after stroke, evoked maps reveal a greatly attenuated $S1_{FP}$ map, which remaps posterior to the infarct by week 4. Likewise, fc maps at week 1 show weakened homotopic connectivity, primarily around the infarct, with recovery of an fc structure similar to baseline by week 4. These results suggest that recovery after stroke is associated with both remapping of $S1_{FP}$ and reintegration of remapped regions into global delta band fc networks. This study will lay the foundation for future work on the molecular and cellular mechanisms underlying network plasticity, which may enable targeted therapy to enhance stroke recovery.



Disclosures: **Z.P. Rosenthal:** None. **J. Lee:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.02/Z6

Topic: C.08.Stroke

Support: Strategic Innovation Fund

Healthier Wisconsin Partnership Program

Title: Whole-brain indirect structural connectivity detects loss of cerebellar connectivity after stroke

Authors: ***M. R. SOTELO**[1], B. D. SCHMIT[2]
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Abstract: Introduction: The impact of a stroke on overall brain connectivity depends on lesion disruption of structural connections in the brain. This structural connectivity has been characterized using diffusion tensor imaging to model white matter integrity; however, these techniques do not take into account whole-brain connectivity. We have developed a novel approach to objectively analyze whole-brain structural connectivity to identify global effects of stroke and uncover underlying mechanisms influencing functional outcome.
Methods: Diffusion MRI scans were obtained using the qball-HARDI, 2mm, 150 directions protocol (b-value=1500 s/mm^2). FMRIB Software Library (FSL) was used for processing the images. Cortical and subcortical regions were segmented from the MNI template using Freesurfer, and cerebellar segmentation was obtained from FSL, resulting in 114 nodes in the brain. Probabilistic tractography using the ball-and-sticks model was performed, and weighted-undirected networks were binarized at sparsity levels from 1-10% of the maximum connectivity. The voxel-wise indirect structural connectivity (VISC) algorithm[1] was implemented on a regional level in MATLAB. A Student's T-test was used to compare the chronic stroke group (n=11) with the control group (n=8). Separately, a percent difference threshold (10%) identified regions with reduced VISC in each subject. At each sparsity level, these regions were group-averaged to show the median for the group.
Results: Structural connectivity identified using this regional application of the VISC metric indicated significantly lower structural connectivity in the cerebellum, pons, and the thalamus in the stroke group. The matrix sparsity had an effect on identifying regions with reduced VISC, showing the importance of using a range of sparsity levels in connectivity matrix analyses. In an individual case, a left basal ganglia and brain stem lesion resulted in lower VISC in the contralesional thalamus and cerebellum. A left cerebellar lesion resulted in reduced VISC in the contralesional cerebellar and on both hemispheric basal ganglia. The median reduction in VISC at the 1% sparsity level showed reduced VISC in the vermis and ipsilesional cerebellum not found in the control group.
Conclusion: Indirect structural connectivity indicated reduced connectivity to cerebellar regions after stroke, suggesting its role in functional outcome.
References:
1. Kalinosky, Benjamin T., Sheila Schindler-Ivens, and Brian D. Schmit. "White Matter Structural Connectivity Is Associated with Sensorimotor Function in Stroke Survivors." *NeuroImage : Clinical* 2 (2013): 767-781

Disclosures: **M.R. Sotelo:** None. **B.D. Schmit:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

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Topic: C.08.Stroke

Support: Alberta Innovates Health Solutions Clinician Fellowship

Canadian Institues of Health Research (MOP 106662)

Heart and Stroke Foundation of Canada Grant-in-aid

Ontario Research Fund Grant (ORF-RE_04-47)

Title: Brain regions associated with motor and proprioceptive recovery after stroke

Authors: *S. E. FINDLATER[1], J. E. TAPPER[2], J. A. SEMRAU[1], J. M. KENZIE[3], A. X. YU[2], T. M. HERTER[4], S. H. SCOTT[5], S. P. DUKELOW[1]
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Abstract: Compared to motor recovery, we know little about sensory recovery after stroke. Recent findings indicate that motor and proprioceptive deficits in the arm recover at different rates after stroke. This has implications for developing targeted treatments. Motor and sensory brain areas are highly connected; however, we query whether anatomical distinctions underlie the differences observed in motor and proprioceptive recovery. Motor and proprioceptive performance was assessed at 26 weeks in 140 subjects after stroke with a KINARM exoskeleton robot. Motor performance was measured with an 8-target centre-out reaching task (Visually Guided Reaching, VGR). Proprioception was assessed with 2 mirror-matching tasks conducted without vision. Position Matching (PM) assesses static limb position sense and Kinesthesia (KIN) assesses limb movement sense. Each task yields a composite task score and several parameter scores that measure speed and spatial errors. Normative control ranges based on 231 healthy subjects were used to determine impairment. Statistical region of interest (sROI) analyses compared motor and sensory performance with stroke lesion location across 150 brain regions using a general linear model. Task Score Maps: Preliminary results revealed that damage to the corticospinal tract (CST) and Heschl's gyrus was associated with poor Task Scores for VGR, PM and KIN. Damage to the postcentral, supramarginal, inferior parietal gyri and arcuate fasciculus was associated with poor Task Scores for PM and KIN. Parameter Score Maps: Unique lesion locations were associated with parameter scores for VGR (Heschl's gyrus and CST lesions were associated with initial direction error; putamen, caudate and CST were associated with poor movement time). For PM, lesions in the Rolandic operculum and insula were associated with poor variability while lesions in the superior parietal lobe and CST were associated with poor perception of workspace area. For KIN, cortical lesions (Heschl's, postcentral, supramarginal, inferior and superior parietal gyri) were primarily associated with poor initial direction error whereas white matter regions (e.g. arcuate fasciculus, optic radiations, CST) were associated with poor response latency scores. Overall, sROI detected differences in brain regions associated with poor motor compared to poor proprioceptive performance. Parameter scores identified more distinct lesion/behaviour relationships. These findings add to evidence that motor and proprioceptive function after stroke are dissociable. Further, these findings may be of use in developing targeted treatments for specific impairments after stroke.

Disclosures: **S.E. Findlater:** None. **J.E. Tapper:** None. **J.A. Semrau:** None. **J.M. Kenzie:** None. **A.X. Yu:** None. **T.M. Herter:** None. **S.H. Scott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BKIN Technologies. **S.P. Dukelow:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.04/Z8

Topic: C.08.Stroke

Title: Efficacy of resting-state biomarkers versus behavioral measures in discriminating hemispatial neglect in stroke patients

Authors: *E. PIRONDINI[1], N. ZINGER[2], L. Y. DEOUELL[3], D. VAN DE VILLE[1]
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Abstract: Hemispatial neglect is a highly heterogeneous perceptual disorder that often follows stroke, especially after right hemisphere lesion. Its most typical characteristic is failure to report or respond to visual, somatosensory, and auditory stimuli presented in the contralesional space. Standard clinical evaluations include “pencil-and-paper” (PnP) tests that consist in drawing and cancelation tasks. Recent studies showed that computer-based assessments have several advantages over PnP tests offering a major methodological improvement in studies of neglect rehabilitation. While computer-assisted measurements reduce the chances for ceiling effects and allow evaluating performance changes through repeated assessments, combination of classical approaches to brain recordings might increase the sensitivity of clinical tests. An increasing number of studies showed that spontaneous brain activity could be of great clinical value potentially providing novel, rich, and sensitive biomarkers to delineate neurological disorders and responses to treatment. In particular, electroencephalography (EEG) recordings are safe, inexpensive, and accessible in complex medical settings and they could, thus, be ideal for biomarkers definition.
Here we aimed at comparing the sensitivity of spontaneous brain activity measured at rest with EEG to a computerized task in discriminating unilateral neglect. As computer-based task, we used the Starry Night Test (SNT), which presented a higher sensitivity than Behavioral Inattention Test at the individual level. Twenty patients between 1 and 3 months post-stroke and 6 healthy control subjects were enrolled in the study. Lesion location was confirmed by Computer Tomography images. EEG activity during resting-state (RS) was recorded before the SNT task. In order to assess the reproducibility of these tests, SNT and RS were repeated

multiple times per day in two different days. Spontaneous alpha and beta oscillations resulted in a higher accuracy (overall accuracy average ± std over days and sessions: 0.88 ± 0.03) in discriminating patients and healthy subjects as compared to reaction time measures from the SNT test (overall accuracy: 0.73 ± 0.03). Moreover, cortical oscillatory activity recorded at rest predicts behavioral deficits in the SNT task.
In conclusion, this data suggests that evaluation of resting-state brain recordings could benefit the evaluations of unilateral neglect beyond traditional PnP and computerized tests. Moreover, resting-state EEG has the potential to provide an index of the dynamics of spontaneous recovery and effects of rehabilitation interventions.

Disclosures: E. Pirondini: None. **N. Zinger:** None. **L.Y. Deouell:** None. **D. Van De Ville:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

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Program#/Poster#: 673.05/Z9

Topic: C.08.Stroke

Support: CIHR MOP-130269

Title: Corpus callosum anatomy in chronic stroke, revealed through structural segmentation

Authors: *J. K. FERRIS, K. S. HAYWARD, J. L. NEVA, L. A. BOYD
Physical Therapy, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Introduction: The corpus callosum (CC) is the principle neural structure mediating interhemispheric interactions. The CC can be subdivided into segments, containing tracts from distinct cortical regions. Previous anatomical subdivisions of the CC have divided this structure into five to ten sections by manual segmentation. However, these divisions do not reflect individual functional or anatomical differences in the CC. After stroke resulting in motor impairment, there is evidence that both descending motor pathways and interhemispheric connections are impacted. Yet, previous studies of individuals with chronic stroke relied on division of the CC into fixed segments, which may underestimate variability in individual anatomy. Here, we use probabilistic tractography to subdivide the CC on the basis of connectivity with cortical targets, in order to determine how CC anatomy is altered in individuals with chronic stroke
Methods: Four groups of individuals (healthy younger adults, healthy older adults, individuals with chronic stroke with mild upper-limb impairment, chronic stroke with severe upper-limb impairment) underwent T1-weighted anatomical, and 60-gradient high-angular resolution diffusion imaging (HARDI) scans on a 3.0T Philips Achieva scanner. MRI analyses were carried

out by tools from FSL and Freesurfer. Bilateral masks of the following cortical targets are being acquired: precentral gyrus, postcentral gyrus, premotor cortex, prefrontal cortex and parietal cortex. Probabilistic tractography will be performed to define connectivity between cortical targets and corpus callosum. The number of voxels within the CC with ≥ 95% probability of connectivity to each cortical target will be calculated. To determine if the number of voxels per CC segment differed between groups, we plan to perform a one-way analysis of variance (ANOVA), with Group as a between subject factor. ANOVAs will be performed separately for each cortical target. To explore the functional relevance of the identified CC segments, fractional anisotropy (FA) of cortical tracts will be related to motor function (Wolf Motor Function Task) and impairment (Fugl-Meyer) using Spearman's correlation coefficients.
Results: Results of the planned analyses will be presented at the 2017 SFN meeting
Conclusions: This analysis will show whether an anatomically determined segmentation of corpus callosum projections is impacted differently by stroke. Our work will reveal nuanced neuroanatomical changes after stroke resulting in mild or severe upper limb impairment, and stands to increase our understanding of how corpus callosum integrity relates to motor outcomes after stroke.

Disclosures: **J.K. Ferris:** None. **K.S. Hayward:** None. **J.L. Neva:** None. **L.A. Boyd:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.06/Z10

Topic: C.08.Stroke

Support: NIH Grant R01NS093057

Title: Investigating the role of contralesional cortex activation in post-stroke recovery

Authors: *M. ITO, M. Y. CHENG, D. L. SMERIN, S. L. LEVY, T. C. CHIANG, G. K. STEINBERG
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Abstract: Background: Functional neuroimaging studies have reported increased activation in the contralesional primary motor cortex (cM1) in both experimental and clinical settings of stroke. However, the cM1 activation with cellular resolution and its role in post-stroke recovery is unclear. In this study, we characterized the time course of active neuronal network after experimental stroke in mice by immunostaining with neuronal activity-dependent markers. Furthermore, we investigated the role of cM1 activation in post-stroke recovery using the chemogenetic inhibitory DREADD system. Methods: Adult male C57Bl6 mice (6-7 weeks) were subjected to stereotaxic injection of AAV-CamKIIa-hM4D-mCherry into the cM1. After 4-5

weeks, ischemic stroke was induced by transient MCAO. For the time course study, mice were sacrificed at post-stroke days (PD) 3, 5, 14 and 28 (n=5, 4, 5 and 3, respectively). Brains were processed for immunostaining using pCREB antibody (neuronal activity-dependent marker). In another cohort, stroke mice received either clozapine-N-oxide (CNO) or saline (SAL) intraperitoneally from PD 5-14. Functional recovery was evaluated using the rotating beam test at pre-stroke baseline and PD 4, 7, 10, and 14. All mice were sacrificed at PD15 for histology. All mice analyzed in this study showed comparable cortico-striatal infarct in the left hemisphere and hM4D-mCherry expression in cM1. Results: After stroke, pCREB was predominantly expressed in cM1 when compared to ipsilesional M1 (iM1). The expression of pCREB in cM1 was observed as early as PD3 and gradually increased at PD5 and 14, indicating interhemispheric imbalance of cellular cortical activity after stroke. Neuronal silencing of cM1 via the inhibitory DREADD (CNO-treated mice) showed a trend of maladaptive effect on functional recovery after stroke when compared to control group (CNO n=5, SAL n=4, P=0.3 (treatment*time), two-way repeated measure ANOVA of speed). Immunohistological staining with pCREB at PD15 showed that CNO-treated mice exhibited reduced cellular activity in cM1, indicating the silencing effect of the hM4D. Conclusions: Our results showed that basal cM1 neuronal activity increased after stroke and interhemispheric cortical imbalance persisted until at least PD14. Chemogenetic inhibition of cM1 during PD5-14 exacerbated recovery, suggesting that early cM1 activation may be beneficial for functional outcome. Current studies investigate the effect of chemogenetic inhibition in late phase after stroke, since activation of cM1 may have time-dependent role. Ongoing studies also examine which neuronal subtypes are predominantly activated in cM1 after stroke.

Disclosures: **M. Ito:** Other; Japan Society for the Promotion of Science. **M.Y. Cheng:** None. **D.L. Smerin:** None. **S.L. Levy:** None. **T.C. Chiang:** None. **G.K. Steinberg:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.07/Z11

Topic: C.08.Stroke

Title: Resting-state functional connectivity changes in photothrombotic ischemic stroke rat model

Authors: *H.-S. LEE, J.-H. YOON, O.-H. CHEONG, S.-H. PARK, Y. JEONG
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Abstract: Introduction: Ischemic stroke is one of the major causes of death and disability. A number of papers have been studied focused on global functional connectivity changes after large, nonspecific ischemic stroke during task and in the resting-state. However, there is no study

on how global resting functional connectivity (rsFc) changes with specific cortical region damage. Photothrombotic ischemic (PTI) stroke is a focal cerebral ischemia model which utilizes a photocoagulation process of Rose Bengal with light at target area. Adjusting the duration of light and dye concentration, focal infarct size is controllable. Here, we focally induced stroke on primary motor cortex (M1) using rat PTI model and examined longitudinal changes in rsFc as well as their motor ability and infarct volume changes. **Methods:** Sprague-Dawley rats were used in this study. Rose Bengal was intravenously injected and cranial windows were made. The animals grouped into PTI and Sham group and light for thrombosis was only illuminated to PTI group on motor cortex (M1). Motor task (Rotarod), and T2-weighted and resting-state fMRI (rsfMRI) scanning with 3T MRI under light isoflurane anesthesia were performed before (day 0) and on 1, 3, and 6 days after thrombosis. Ischemic volumes were measured with T2-weighted images and functional connectivity was assessed with rsfMRI. **Results:** On Rotarod, PTI group showed significantly decreased latency on day 1 but progressively recovered on days 3 and 6. The infarct size also gradually reduced to half the size of day 1 on day 6. rsfMRI results showed reduced functional connectivity in 64 whole brain regions of interest (ROIs) on day 1, especially with M1 and gradually improved with recovery. Accordingly, network theory based analysis revealed disrupted network properties in the PTI group. All properties were recovered simultaneously with recovery. **Conclusions:** After photothrombosis on M1, motor performance and functional connectivity of M1 were significantly decreased. Afterward they were recovered in some degree without any treatment. Our results showed that focal lesion can induce changes of global functional connectivity and the changes are related with behavioral performance. Further research on relationship between recovery and functional connectivity by local damage will provide knowledge on better motor rehabilitation.

Disclosures: H. Lee: None. **J. Yoon:** None. **O. Cheong:** None. **S. Park:** None. **Y. Jeong:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

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Program#/Poster#: 673.08/Z12

Topic: C.08.Stroke

Support: Global Ischemia Foundation

Department of Molecular and Integrative Physiology

Title: Elevated functional connectivity within injured cortical regions after focal stroke

Authors: *F. TIAN[1], T. SHICK[1], A. SAJJAD[1], M. WANG[1,2], J. BORJIGIN[1]
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Abstract: Focal stroke, one of the major causes of mortality and morbidity, affects millions of individuals around the world. Very little, however, is known about the temporal changes in the intrinsic electrical activity of the brain following focal stroke. The objective of this study is to explore how the injured region interacts with the healthy region of the brain during focal stroke. A total of 10 Sprague Dawley rats were included in this study. Baseline EEG (from 8 cortical loci) and EKG signals were recorded for 1 hour. Online recording was continued for a maximum of 20 hours after right middle cerebral artery occlusion (RMCAO). All rats showed large infarcts on the right side of the brain, half of which died suddenly with a mean survival length of 13.58 hours. Dead rats were found to have suffered subarachnoid hemorrhage (SAH), in addition to the ischemic stroke. In all 10 rats following RMCAO, there was a marked reduction of EEG power for all 8 EEG channels. As expected, all 4 channels located on the right side of the brain (injured side) demonstrated more significant reduction of EEG power than the left side, especially for the site of injury. EEG coherence (functional connectivity) for signals recorded from the left side of the brain gradually decreased after RMCAO. Interestingly, EEG coherence gradually increased after the stroke on the right side of the brain. In addition, heart rate variability showed distinct patterns in rats that died versus those that survived, suggesting that the autonomic nervous system regulation is different in these two conditions. This study is expected to contribute to our understanding on the temporal dynamics of cortical power, functional connectivity, and the regulation of autonomic nervous system during focal stroke.

Disclosures: F. Tian: None. **T. Shick:** None. **A. Sajjad:** None. **M. Wang:** None. **J. Borjigin:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

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Topic: C.08.Stroke

Support: ERC advanced grant NOGORISE 294115

SNF Grant No. 31003A-149315-1

Title: Optogenetic stimulation of the intact corticospinal tract after stroke restores motor control through regionalized functional circuit formation

Authors: *A.-S. WAHL[1], U. BÜCHLER[2], A. BRÄNDLI[3], B. BRATTOLI[2], S. MUSALL[4], H. KASPER[4], B. V. INEICHEN[3], F. HELMCHEN[4], B. OMMER[2], M. E. SCHWAB[3]
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Abstract: Motor impairment is one major symptom of patients after cortical strokes. Current neuromodulatory strategies to enhance motor recovery often target large brain areas non-specifically and without sufficient understanding of their interaction with internal repair mechanisms. Here we developed a novel therapeutic approach in an animal model of stroke by specifically activating corticospinal circuitry using optogenetics. Rats were subjected to a photothrombotic stroke destroying >95% of the sensorimotor cortex. Optogenetic stimulation of corticospinal neurons, in combination with intense subsequent rehabilitation, led to full recovery of lost motor functions, similar to an Anti-Nogo immunotherapeutic approach. A new computer vision based automatic behavior analysis revealed that recovery in a grasping task represented true restoration of baseline movement patterns rather than compensatory actions. Optogenetic stimulation of the corticospinal neurons induced their axona to sprout from the intact to the denervated cervical hemi-cord. In recovered animals, optogenetic silencing of these corticospinal projection neurons in premotor and primary motor area resulted in too long or too short targeting movements of the restored grasping function, thus identifying the reestablishment of specific and anatomically localized cortical microcircuits induced by successful rehabilitative strategies. These results provide a conceptual framework to improve established clinical techniques such as transcranial magnetic or transcranial direct current stimulation in stroke patients.

Disclosures: A. Wahl: None. **U. Büchler:** None. **A. Brändli:** None. **B. Brattoli:** None. **S. Musall:** None. **H. Kasper:** None. **B.V. ineichen:** None. **F. Helmchen:** None. **B. Ommer:** None. **M.E. Schwab:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.10/Z14

Topic: C.08.Stroke

Title: Automated assessment of dynamic changes in the cortical vascular network architecture after ischemic stroke

Authors: *R. RUST[1,2], M. E. SCHWAB[1,2]
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Abstract: Recovery after stroke can occur by compensation of lost capabilities by functionally related regions or restoration of the functionality of the perilesional, partially affected cortical tissue in the ischemic penumbra. The latter mechanism strongly depends on the revascularization of the ischemic border zone, a process which significantly contributes to the final lesion size and the severity of the clinical deficit. We developed a multi parametric system to reliably analyze dynamic changes and their consequences in the cortical vascular network including (1) stroke size, (2) blood vessel density and distribution (3) neoangiogenesis, (4) perfusion of vessels, and (5) behavior. We evaluated different vascular endothelium-specific antigens (CD31, Glut1, Isolectin B4, Laminin, and Collagen IV) together with the proliferation marker EdU to measure neo-angiogenic activity and distribution. Perfusion of vessels was assessed by a set of intracardially applied vascular tracers (dextran, lectins, and albumin) that were compared on the basis of penetration depth and leakage into the tissue. These tracers can be combined with genetic mouse models with fluorescent markers in the vascular endothelium. A big advantage of transgenic marker mice is the compatibility for 3D applications with cleared whole brain samples that require no additional immunohistochemistry. All data are analyzed automatically with the public domain software ImageJ in an unbiased, trackable and time saving approach to determine the vascular network architecture and its dynamic changes following an ischemic event as well as therapeutic interventions, e.g. with anti-Nogo-A antibodies.

Disclosures: R. Rust: None. **M.E. Schwab:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

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Program#/Poster#: 673.11/Z15

Topic: C.08.Stroke

Support: KAKENHI 15K16361

Title: Compensation of the cortico-reticular tract against cortico-rubral tract block after capsular hemorrhage in intensive rehabilitation-induced recovery

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Abstract: Various forms of reorganization are often shown in the residual central nervous system after cortico-spinal tract (CST) lesion by stroke, which could be enhanced by the poststroke rehabilitation. We reported that forced impaired limb use (FLU) increased the sprouting of the cortico-rubral tract (CRT) in CST-damaged intracerebral hemorrhage (ICH) resulting in the recovery of disturbed forelimb functions. However, the precise role of the CRT in FLU-induced functional recovery is still unclear. To clarify the question, we selectively blocked CRT at the chronic or the early phase after FLU following to ICH and then compared the FLU effect on functional recovery. The FLU effect on the recovery was also investigated in CRT selective blockage during FLU. To block CRT selectively, adult male Wistar rats were first injected lentivirus vector (NeuRet-TRE-EGFP.eTeNT) into the red nucleus and adeno-associated virus vector (AAVdj-CaMKII-rtTAV16) into the ipsilateral motor cortex. Thus, CRT neurons were double-infected, enabling to block synaptic transmission by doxycycline (DOX) administration. Four weeks after virus injections, ICH was made by collagenase injection into the internal capsule, and FLU was given at 1-8 day after ICH. DOX was orally administered for all rats on days 1-28 (during FLU) or 13-20 (early phase) or 92-99 (chronic phase). Skilled reaching task was perfomed as behavioral assessments. ICH rats demonstrated severe impairment of motor function at 24 hours after ICH. In case of the CRT block in the chronic phase, the recovered forelimb function was severely impaired. FLU-induced functional recovery was similarly blocked in CRT block in the early phase. However, in the CRT blockade during FLU, FLU-induced regain of forelimb function was not disturbed. Histological analysis revealed that the change of neurite projection was not observed in CRT, but the cortico-reticular projection was significantly increased. Data suggest that the CRT is a promising substrate for poststroke rehabilitation, but CRT could be quickly compensated by other descending projections such as the cortico-reticular tract.

Disclosures: **A. Ishida:** None. **Y. Ueda:** None. **K. Kobayashi:** None. **T. Isa:** None. **H. Hida:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.12/Z16

Topic: C.08.Stroke

Title: Changes in functional connectivity due to repeated transcranial magnetic stimulation and botulinum toxin treatment-Discussion on two cases with different functional connectivity changes-

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Abstract: Introduction
Concomitant treatment with repeated transcranial magnetic stimulation (rTMS) and botulinum toxin was administered for upper limb paralysis in two patients with chronic stroke. Examination of the functional connectivity (FC) before and after treatment revealed contrasting changes. We report these cases with consideration.
Materials and Methods
The subjects were two patients with chronic stroke: case 1, a man in his sixties with left brain-stem hemorrhage; case 2, a man in his fifties with left putaminal hemorrhage. Prior to admission, botulinum toxin was administered to the paralyzed side of the upper limb flexor muscles. After that, a 2-week intensive in-hospital treatment was administered. In the morning and afternoon, low-frequency rTMS was performed in the unimpaired brain followed by task-orientated training. Before and after the treatment, upper limb function assessments such as Wolf motor function test (WMFT), simple test for evaluating hand function (STEF), and modified Ashworth scale (MAS) were used. FC imaging was performed using 1.5T optimaMR360 (GE Co., Inc.). The conditions for the imaging before and after the treatment were T2-weighted EPI, TR/TE/FA = 3000/40/90, resting-state eyes-open visual fixation, and imaging time of 5 min. For the analysis, band-pass-filter (0.008-0.09 Hz) and linear trend removal were performed after the pretreatment; FC with each anatomical brain site was calculated with the primary motor cortex of the damaged hemisphere (M1) as the starting point. Further, rsfMRI imaging was performed in 10 healthy adult volunteers under the same conditions.
Results
In both cases, WMFT, STEF, and upper limb function improved. In MAS, case 1 showed no notable change, while attenuation of spasms centered in the elbow joint flexor was observed in case 2. In the pretreatment/post-treatment, FC between the right and left primary motor cortices improved to 0.11/1.01 in case 1, but decreased to 0.86/0.35 in case 2.
Discussion
In case 1, there was no change in MAS, and FC increased; thus, interhemispheric interaction was normalized by rTMS. In case 2, MAS improved, but FC decreased; hence, attenuation of spasms by botulinum toxin treatment was involved in the improvement of upper limb function. Motor function prior to treatment was similar for both cases, and despite receiving the same treatment procedure, FC showed contrasting changes. These results demonstrated that even when motor function is almost the same, the FC pattern differs according to the site of injury. Moreover, in treatments for normalizing interhemispheric interaction, such as rTMS, attention needs to be paid to FC before the treatment.

Disclosures: R. Sakai: None. **T. Ishikura:** None. **Y. Kobayashi:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.13/Z17

Topic: C.08.Stroke

Support: JSPS KAKENHI Grant Number 16K19995

Title: Correlation between brain microstructure revealed by NeuriteOrientation Dsipersion and Density Imaging and cerebral hemodynamics and metabolism measured with positron emission tomography in patients with moyamoya disease

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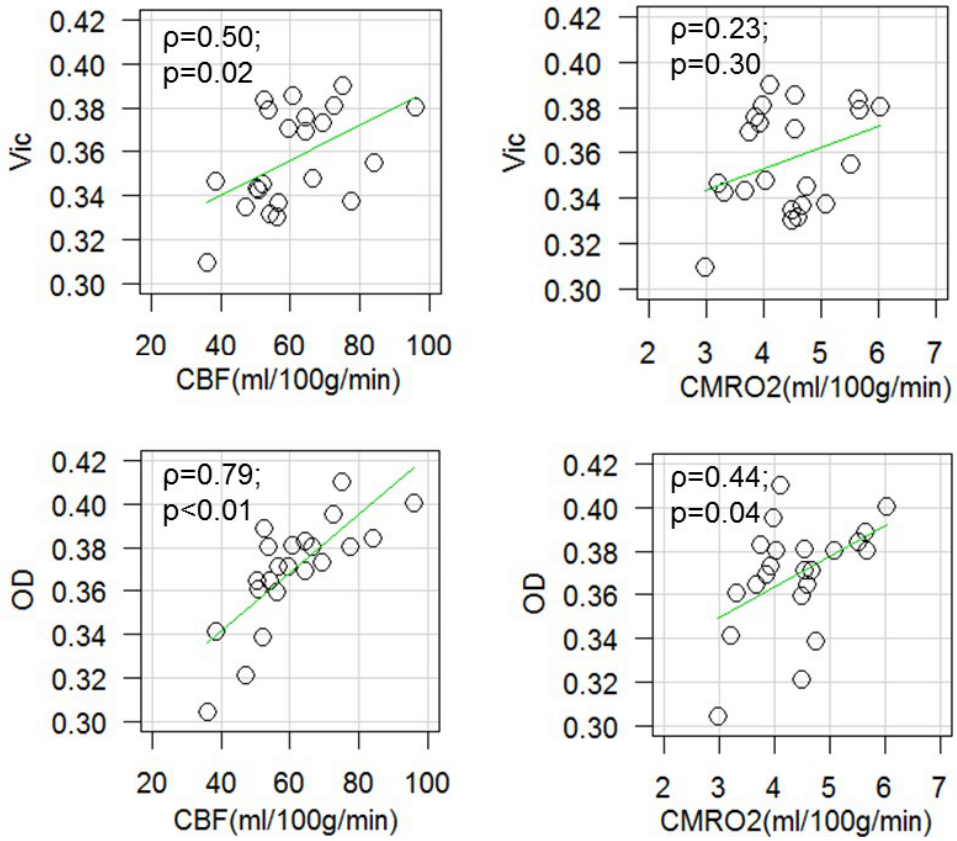
Abstract: *Purpose*: Neurite Orientation Dispersion and Density Imaging (NODDI) is a diffusion MRI model which can evaluate brain microstructure excluding the influence of water component. We investigated the correlation between NODDI measured brain microstructure and PET measured cerebral hemodynamics and metabolism in patients with moyamoya disease, a progressive occlusive cerebrovascular disease that usually cause chronic cerebral ischemia in younger population.*Methods:* From Sep 2015 to Jan 2017, 11 consecutive patients with moyamoya disease underwent 15 O gas positron emission tomography (PET) and MRI. By the analysis of the clinical presentation and the morphological MRI, all hemispheres were categorized as affected (A) or non-affected (N) by the attending neurosurgeon. The diffusion MRI was acquired using a 3.0-T MRI system with 3 b values (0, 700: 30axes, 2850: 60 axes) and fitted to the NODDI model by the NODDI Matlab Toolbox. PET data were acquired using a Discovery 710 PET/CT scanner with inhalation of [15O]CO2 and [15O]O2. Hemispheric cortical ROIs were created from T1 weighted-images in each patient.*Results*: Intracellular volume fraction (Vic) and Orientation Dispersion Index (OD) of NODDI revealed significant correlation with cerebral blood flow (CBF) and metabolic rate of oxygen (CMRO2) in the cortex (Figure1). OD of affected hemispheres were significantly lower than unaffected hemispheres. Discussion: Vic and OD is presumed to correlate with the neuronal density and the network complexity of dendritic spines, which reported to decrease by chronic ischemia. It is reasonable that the decreased CBF lead to decreased Vic, OD and CMRO2, and that OD was lower in the affected hemispheres than in the non-affected ones. It is noteworthy that noninvasively obtained brain microstructure status by NODDI correlated well with cerebral hemodynamics and metabolism which can only be evaluated by 15 O gas PET. *Conclusions*: NODDI may reveal the

progressive neuronal damage caused by chronic ischemia , which is undetectable by the conventional MRI in patients with moyamoya disease.



Disclosures: **S. Hara:** None. **M. Hori:** None. **M. Inaji:** None. **T. Maehara:** None. **K. Ishii:** None. **S. Aoki:** None. **T. Nariai:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

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Program#/Poster#: 673.14/Z18

Topic: C.08.Stroke

Support: NIH Grant NSO89069

Schmidt Program

Title: Trans-synaptic retrograde retinal ganglion cell degeneration after stroke coincides with the stable blind field and with areas of decreased representation in V1

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Abstract: Stroke in the territory of the posterior cerebral artery leads to blindness in all or part of the contralesional visual field. While about 50% of patients experience some degree of visual recovery within the first 6 months after stroke, only 12.5% recover completely (Tiel K., Kolmel, 1990). One limiting factor that may prevent further visual recovery is trans-synaptic retrograde degeneration of retinal ganglion cells (RGC), which has been observed in stroke patients starting as early as 3 months after stroke (Jindahra, Petrie, & Plant, 2009, 2012; Park, Park, Cho, & Park, 2013; Tanito & Ohira, 2013; Yamashita & Miki, 2012). It is still unknown, however, whether RGC complex thinning after stroke is localized to areas of the retina that correspond (retinotopically) to damaged cortical regions. Here we bring into register optical coherence tomography of RGC complex thickness, perimetry, and functional magnetic resonance imaging of visual cortex activity by dividing visual space into the same 12 wedges for all three measures. In both a cross-sectional and a longitudinal study of recent stroke patients (within 1.5 years since stroke) we found that RGC degeneration after stroke occurs across the entire macula, but at a significantly faster rate in areas of the macula corresponding to the blind field. In addition, variability in RGC degeneration across sub-regions of the macula can be explained by the number of active voxels in visual cortex that maximally responded to visual stimulation in the corresponding regions of the visual field. RGC degeneration is negatively correlated with the number of active voxels in visual cortex in all locations, but the relation was significantly stronger for blind areas of the visual field. These results suggest that attempts to increase residual visual cortical activity may prevent RGC degeneration, which could remove one of the barriers to and lengthen the window of spontaneous visual recovery.

Disclosures: C.L. Schneider: None. **E.K. Prentiss:** None. **Z.R. Williams:** None. **B. Sahin:** None. **B.Z. Mahon:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.15/Z19

Topic: C.08.Stroke

Title: The ATLAS (anatomical tracings of lesions after stroke) Dataset

Authors: *J. M. ANGLIN[1], N. BANKS[1], M. SONDAG[1], K. ITO[1], H. KIM[1], J. CHAN[1], J. ITO[1], C. JUNG[1], S. LEFEBVRE[1], W. NAKAMURA[1], D. SALDANA[1], A. SCHMIESING[1], C.

TRAN[1], D. VO[1], P. HEYDARI[1], B. KIM[1], N. KHOSHAB[2], L. AZIZ-ZADEH[1], S. C. CRAMER[2], J. LIU[3], S. SOEKADAR[4], L. T. WESTLYE[5], J. WANG[3], C. J. WINSTEIN[1], C. YU[3], M. LAKICH[6], A. PIENTA[7], A. STROUD[7], S.-L. LIEW[1]
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Abstract: Stroke is a leading cause of adult long-term disability worldwide. Large-scale neuroimaging studies have shown promise in identifying robust biomarkers of stroke recovery. However, analyzing these large datasets is problematic due to barriers in accurate stroke lesion segmentation. Lesion segmentation allows us to account for the size, location and number of each individual's lesions and to understand how these factors impact recovery. Manually traced lesions are the gold standard for lesion segmentation, but require anatomical expertise and can be prohibitively time consuming. While algorithms have been developed to automate this process, the results often lack accuracy. Promising newer algorithms employ machine learning techniques, but these require large training datasets to optimize performance.
To address these issues, we developed ATLAS (Anatomical Tracings of Lesions After Stroke), a publically-available dataset of 316 manually segmented lesions on T1-weighted MRIs with metadata. This large, diverse dataset can be used to train and test lesion segmentation algorithms and act as a standardized dataset for comparing the performance of different segmentation methods.
ATLAS lesions were traced by a team of 11 individuals. All team members were trained by an expert tracer on an identical set of lesions and followed detailed written and video protocols. We assessed inter- and intra-rater reproducibility by averaging the dice correlation coefficient (DCC) between and within tracers, across the lesion training set (inter-rater DCC = 0.76±0.17; intra-rater DCC = 0.83±0.13). All lesion segmentations were quality checked by a second tracer. An experienced neuroradiologist reviewed all lesions to create metadata, including the number and location of lesions (left/right hemisphere; cortical/subcortical), type of stroke (embolic, hemorrhagic), primary stroke location, vascular territory, and severity of periventricular and deep white matter hyperintensities. This metadata allows for sorting of the ATLAS dataset based on specific categories of stroke, and provides lesion characteristics during the evaluation of algorithms (e.g., an algorithm might fail primarily on cortical lesions, or in brains with multiple lesions, etc.).
ATLAS is deposited on the Archive of Data on Disability to Enable Policy (ADDEP) and hosted by the Interuniversity Consortium for Political and Social Research (ICPSR), the world's largest social science data achieve, which supports rehabilitation. We anticipate that ATLAS will become a useful resource to standardize the segmentation protocol, and improve the accuracy of current lesion segmentation methods.

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Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.16/Z20

Topic: C.08.Stroke

Support: NIH Grant AG042189

NIH Grant NS074895

Title: Retrograde Neurodegeneration of Substantia Nigra Projections to the striatum following long term survival after Ischemic Stroke

Authors: *A. PANTA, F. SOHRABJI
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Abstract: Introduction: Stroke survivors suffer from long-term physical, cognitive and affective disabilities. These disabilities lower the quality of life, contribute to social isolation and anhedonia, and clinical disorders such as post-stroke depression (PSD), which disproportionately affects women. Preclinical studies show that lesions of the substantia nigra (par compacta) impair both motor performance and reward seeking behavior. Neurons from the SNc project to the striatum, a region that is significantly infarcted by middle cerebral artery occlusion (MCAo).
Hypothesis: Ischemia induced by MCAo leads to retrograde degeneration of the SNc pathway projecting to the striatum.
Methods: Middle-aged Sprague-Dawley female rats (12 months old) were subjected to ischemic stroke using a silicon-coated nylon filament suture to occlude the middle cerebral artery (MCA) which was removed 75min after to allow for reperfusion. After 14 weeks of survival, rats were again anesthetized and Fluorogold (Flg) was injected into the left and right striatum. Four days later, animals were overdosed with anesthetic, perfused with saline and formaldehyde and the brain removed for cryosectioning. In three sections per animal, Flg-labeled cells in the SNc were counted on both hemispheres, using fluorescent illumination.
Results: Flg-injections into the striatum retrogradely labeled neurons in the midbrain. There was a 35% decrease ($p<0.009$) in the number of Flg labeled SNc cells in the ischemic hemisphere (85.5+18.2) as compared to the non-ischemic hemisphere (132.4+22.7). The reduced number of projection neurons in the ischemic henmisphere is consistent with the loss of trophic support from the striatum.
Conclusions: SNc neurons are a critical component of reward pathway and motor function,

hence degeneration of these neurons could lead to long term motor deficits and depressive symptoms including anhedonia that are common after stroke.

Disclosures: **A. Panta:** None. **F. Sohrabji:** None.

Poster

673. Stroke: Functional Connectivity Changes in Animals and Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 673.17/Z21

Topic: C.08.Stroke

Support: NIH/NINDS Intramural Research Program

Title: Unmasking the complex systems biology of tissue remodeling after ischemic brain injury in rats using multiplex fluorescence biomarker immunohistology and multispectral imaging

Authors: *D. MARIC, J. D. BERNSTOCK, A. B. SEDLOCK, Y. MOU, D. YE, J. M. HALLENBECK
NINDS/NIH, Bethesda, MD

Abstract: Stroke is a leading cause of death in the United States and even when non-lethal it can lead to complex and widespread debilitating changes in the brain, with marked deterioration of quality of life and potentially long recovery times required to restore lost functions. While extensive stroke research conducted thus far has aimed to better characterize the complex processes mediating brain tissue damage and recovery after stroke, our full understanding of these processes and designing comprehensive drug treatments to elicit most beneficial clinical outcomes are still in their nascent stages. To further advance this field of research, we used a systems biology approach by combining large-scale multiplexed fluorescence immunohistology of rat brains after focal ischemic injury with whole brain slide scanning using a customized multispectral imaging platform. We processed 10-micron thick serial whole brain coronal sections collected from male Sprague Dawley rats at 72 hours following focal brain ischemia using a medial cerebral artery occlusion (MCAO) model. Sections were repeatedly probed and sequentially imaged using a panel of up to 50 fluorescent biomarkers relevant to cellular and molecular processes mediating neuroinflammation, neuroplasticity, neurogenesis, gliogenesis and angiogenesis in response to MCAO. Unique combinations of these biomarkers enabled a comprehensive identification and quantitation of all relevant cell types (neurons, astrocytes, oligodendrocytes, endothelial cells, microglia, immune cells, etc.) and their changing functional states (reactive, resting, apoptotic, proliferative, etc.) in the brain after injury. The results show dynamic and highly complex spatiotemporal changes in brain tissue remodeling and recovery after ischemic injury eliciting distinct cellular/molecular and specific niche responses that develop both proximally and distally to the site of injury. This work demonstrates the crucial

need and a workable solution to apply comprehensive multiplex fluorescence biomarker screening and multispectral imaging to study the systems biology of brain in response to ischemic injury. The practical computational solutions pertaining to processing very large image datasets (including those involving multiplex 3D imaging of the entire brain using array tomography) and multi-parametric computational image analysis of these datasets are currently in development.

Disclosures: D. Maric: None. **J.D. Bernstock:** None. **A.B. Sedlock:** None. **Y. Mou:** None. **D. Ye:** None. **J.M. Hallenbeck:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.01/Z22

Topic: C.08.Stroke

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

American Heart Association, AHA Award #16POST27710039

Title: Neuroplasticity mechanisms that lead to stroke recovery

Authors: *M. T. JOY[1], A. J. SILVA[2], S. T. CARMICHAEL[3]
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Abstract: Stroke is the leading cause of long-term adult disability in the US. With the exception of clot busting drugs (tPa) and endovascular therapies, neurorehabilitation is the only therapy in clinical use. Pharmacological attempts to improve recovery have included the use of molecular effectors of neuroplasticity as targets. Molecular mechanisms that underlie stroke recovery remain largely unknown. C-C chemokine receptor 5 (CCR5) was recently identified as a regulator of synaptic plasticity in hippocampal learning and memory circuits[1]. We investigated if CCR5 signaling regulates stroke recovery. We show that CCR5 knockdown in specific motor circuits induces early and sustained motor recovery following an ischemic stroke in the motor cortex. Pharmacological blockade of CCR5 also produces similar recovery effects in motor function, paving the possibility of using CCR5 as a druggable target for stroke recovery. The mechanism through which CCR5 signaling augments changes in synaptic plasticity effecting recovery were investigated. As CCR5 knockdown leads to early recovery, within the first week of stroke, we monitored changes in dendritic spine dynamics in pre-motor cortex, anterior to the stroke site. Our data shows that CCR5 knockdown reduces spine loss and preserves ~80% of

dendritic spines when compared to control-stroke groups that showed a 50% loss of spines. Moreover, CCR5 knockdown induces robust changes in structural plasticity. Using a quantitative cortical mapping approach, our data shows that CCR5 knockdown causes sprouting of axons into the contralateral hemisphere from pre-motor cortex ipsilateral to the stroke site. Taken together, our data shows that CCR5 knockdown induces changes in synaptic plasticity that underlie motor recovery post-stroke, acting as a potent target for stroke recovery. Reference 1. Zhou M, Greenhill S, Huang S, Silva TK, Sano Y, Wu S, et al. CCR5 is a suppressor for cortical plasticity and hippocampal learning and memory. Elife. 2016;5.

Disclosures: **M.T. Joy:** None. **A.J. Silva:** None. **S.T. Carmichael:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.02/Z23

Topic: C.08.Stroke

Support: European Union's Horizon 2020 Grant 720270

H2020 EXCELLENT SCIENCE - European Research Council (ERC) Grant 692943 BrainBIT

Title: Optogenetic rehabilitation promotes functional remodelling after stroke: An *In vivo* imaging study

Authors: *E. CONTI[1], A. L. ALLEGRA MASCARO[1,2], F. RESTA[1], E. QUARTA[1], L. SACCONI[1,3], S. LAI[4], S. MICERA[4,5], F. S. PAVONE[1,3,6]
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Abstract: Neuro-rehabilitative research is developing novel strategies to enhance the effectiveness of therapies after stroke by using physical and plasticizing treatment. Previous studies have shown that repeated neuronal stimulation of the peri-lesioned area with optogenetics induces a significant improvement in cerebral blood flow and neurovascular coupling response. Up to now the mechanisms underneath the reshaping of brain circuitry induced by rehabilitation after stroke are still unknown. By performing *in vivo* imaging of Thy1-GCaMP6f mice we want to investigate how different rehabilitative therapies shape new cortical maps in the peri-infarct area. In order to promote the functional recovery after stroke we use either an optogenetic

strategy to stimulate targeted excitatory neurons in the peri-lesional region or motor training on a robotic platform. In the first case, we repeatedly stimulate with a 473 nm laser ChR2-transfected neurons five days a week. In the second paradigm, we investigate the effects of motor rehabilitation by performing wide field cortical imaging while the animals execute a motor task on a robotic device. We investigate how light-stimulation moulds cortical maps, and compared it with remodelling induced by motor training. We analyse the spatio-temporal calcium dynamic and the reshaping of cortical activation area during the movement in a month. We then evaluated how the interhemispheric connectivity changes in response to the different rehabilitation approach. Our combination of techniques allows obtaining unprecedented views on cortical plasticity induced by rehabilitative therapies.

Disclosures: E. Conti: None. **A.L. Allegra Mascaro:** None. **F. Resta:** None. **E. Quarta:** None. **L. Sacconi:** None. **S. Lai:** None. **S. Micera:** None. **F.S. Pavone:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.03/Z24

Topic: C.08.Stroke

Support: Health Research Council of New Zealand 14/136

Title: Does tonic inhibition in the sub-acute period after stroke alter the trajectory of upper limb recovery?

Authors: *J. CIRILLO[1,2], R. A. MOONEY[1,2], V. M. BORGES[2,3], P. A. BARBER[2,3], A. N. CLARKSON[4], S. J. ACKERLEY[2,3], M.-C. SMITH[2,3], C. MANGOLD[2], C. M. STINEAR[2,3], W. D. BYBLOW[1,2]
[1]Dept. of Exercise Sci., [2]Ctr. for Brain Res., [3]Dept. of Med., Univ. of Auckland, Auckland, New Zealand; [4]Dept. of Anat., Univ. of Otago, Dunedin, New Zealand

Abstract: Evidence from experimental animal models of stroke indicates that reducing the level of tonic inhibition present in motor cortex may facilitate neural plasticity, learning, and motor recovery. The present study is examining primary motor cortex (M1) inhibition in patients over the first 12 weeks after stroke, and in a cohort of age-similar healthy controls. Gamma aminobutyric acid (GABA) concentration and neurotransmission in M1 are assessed using magnetic resonance spectroscopy (2 and 6 weeks after stroke) and threshold tracking paired-pulse transcranial magnetic stimulation (TMS) (2, 6, and 12 weeks after stroke). Upper limb impairment is assessed with Fugl-Meyer Upper Extremity Scale at 2, 6, 12 and 26 weeks after stroke. Similar to recent studies, patients with a functionally intact corticospinal pathway exhibit

a proportional recovery such that upper limb impairment resolves by ~70% of the maximum possible. MRS indicates that compared to age-similar controls, GABA concentration are reduced within contralesional, but not ipsilesional, M1 6 weeks after stroke. Short- and long-latency intracortical inhibition examined with TMS indicate greater inhibition in the ipsilesional hemisphere during the spontaneous recovery period after stroke compared to controls. Patients with higher tonic inhibition in ipsilesional M1 tend to have a longer recovery period. The extent of postsynaptic GABAergic inhibition is similar to controls during the early spontaneous recovery period, but disinhibition is present by 12 weeks post-stroke. These findings indicate that the ability to modulate tonic inhibition levels early after stroke may have implications for upper limb recovery during the spontaneous recovery period.

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Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.04/Z25

Topic: C.08.Stroke

Title: Position and movement sense in stroke patients; pilot study

Authors: *Y. ACOSTA-SOJO, B. J. MARTIN
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Abstract: Asymmetries in upper limb position and movement sense have been identified in healthy participants. However, traditional and current rehabilitation procedures have ignored intrinsic asymmetries and rarely differentiate the specific sensory and/or motor needs after stroke. The brain damage suffered during the stroke can limit the functionality of the right and left hemisphere of the brain, causing motor and sensory deficits. As a result, alteration of asymmetries observed in healthy patients is expected to occur in stroke patients. For this reason, the aim of this pilot study was to investigate the alteration of sensory information received from the same or opposite limb/hemisphere system in mildly/moderately affected stroke patients. The sensory system was tested by proprioceptive perception of upper limb position and movement. Position sense was tested with eyes closed while participants matched a reference position imposed by a robotic arm in two different conditions: ipsilateral remembered and contralateral concurrent. Movement sense was tested with eyes closed while participants matched with the opposite arm the perceived movement elicited by a vibration applied to the triceps of the reference arm. The preliminary results indicate an exacerbation of position and movement sense

asymmetry between the right and left limb systems. The matching position errors are greater for the affected limb when the matching and reference movements are performed with the same limb and matching errors are greater when memorization of perception is required. The amplitude and velocity of movement matching vibration-induced illusion is lower for the affected than non-affected limb. It is worth noting that "greater error and exacerbation" are to be considered in the context of intrinsic asymmetries in healthy controls.

Disclosures: Y. Acosta-Sojo: None. **B.J. Martin:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.05/Z26

Topic: C.08.Stroke

Title: Tailoring non-invasive brain stimulation to enhance bimanual arm coordination in individuals with chronic stroke

Authors: *W. LIAO[1], J. WHITALL[1], J. E. BARTON[2], S. MCCOMBE WALLER[1]
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Abstract: Using non-invasive brain stimulation (NIBS) as an adjunctive therapy has become increasingly popular in stroke rehabilitation. Current protocols have focused on the interhemispheric competition model which emphasizes facilitation of the lesioned hemisphere or inhibition of the non-lesioned hemisphere. Few studies have examined the effects of NIBS on bimanual arm function. The purpose of this study was to examine the neuro-modulation effects of ipsilesional primary motor cortex (iM1) vs. contralesional dorsal premotor cortex (cPMd) on interlimb coordination and cortical function in individuals with chronic stroke. We hypothesized that subjects would show differential responses to these two types of stimulation and that these differences may be associated with their level of paretic arm function. **Subjects:** Eight subjects with chronic stroke. **Methods:** Using a repeated measures design, subjects received a single session of 5Hz repetitive transcranial magnetic stimulation (rTMS) on either iM1 or cPMd. During each session, subjects performed isometric elbow flexion tasks with a single arm or both arms while matching a visual target corresponding to 20% of their maximal voluntary contraction. Outcomes included motor evoked potential amplitude (MEPs) of M1 bilaterally, force performance, and muscle coherence of the two arms during the bimanual task. **Results:** Six subjects showed greater MEP amplitudes in the lesioned M1, and decrease of MEPs in the non-lesioned M1 after iM1 stimulation ($p<.05$). Muscle coherence between two arms during the bimanual task also increased after iM1 stimulation ($p<.05$). In contrast, two subjects

demonstrated greater MEP amplitudes in the lesioned M1 after cPMd compared to iM1 stimulation. Muscle coherence between the arms during bimanual tasks also increased after cPMd, but not iM1 stimulation. A regression model showed the percentage change of MEP amplitude of lesioned M1 was significantly correlated with distal arm function of Fugl-Meyer assessment scores (p=.03, R^2=.63). **Conclusion:** Our study identified two different patterns of response after rTMS to iM1 and cPMd in subjects with chronic stroke. Subjects with more impaired distal arm function, may benefit more from direct enhancement of cPMd than lesioned M1. Our preliminary findings indicate that protocols of NIBS should be individualized to each subject.

Disclosures: W. Liao: None. **J. Whitall:** None. **J.E. Barton:** None. **S. McCombe Waller:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.06/Z27

Topic: C.08.Stroke

Title: Exercise ameliorates the effects of compensatory limb training in a mouse model of stroke

Authors: *A. L. KERR, E. M. HAAN, R. MAVROS, V. NEMCHEK
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Abstract: Stroke is a leading cause of disability worldwide. However, current rehabilitative therapies are insufficient in restoring pre-injury function. Upper-limb deficits are among the most common, chronic deficits associated with stroke. A common consequence of this deficit is compensatory over-reliance on the less-impaired limb (contralateral to the injured hemisphere). However, previous research in humans and animal models suggests that these post-stroke compensatory behaviors limit the recovery potential of the impaired limb. The current study was conducted using a mouse model of stroke to investigate the impact of aerobic exercise on the ill effects of compensatory limb training. C57BL/6 mice were trained pre-operatively with their preferred limb on the Pasta Matrix Reaching Task (PMRT) to establish skilled reaching behavior (18-20 days). All mice then received a unilateral ischemic stroke (photothrombotic) of the sensorimotor cortex contralesional to the trained limb. Four days after lesion, reaching performance (preferred limb/ impaired limb) was assessed on the PMRT. Mice were then equally divided into three groups: compensatory limb training (CLT), exercise and compensatory limb training (Ex-CLT), and control. Mice were trained in these groups for 14 consecutive days (post-operative training). Mice in the Ex-CLT group had 22-hour access to running wheels in their home cage during post-operative training. Animals receiving CLT training received a daily

training session (PMRT) of their less-impaired limb during the same period. Control animals spent an equivalent amount of time in reaching chambers but were not trained with either limb during post-operative training. Following post-operative training, all mice received daily assessment of the impaired limb (contralateral to the lesion) for five consecutive days (PMRT). Our results indicate that aerobic exercise ameliorates the negative effects of compensatory limb training and permits functional recovery of the impaired limb when paired with focused training of the less-impaired limb. Aerobic activity may be an effective adjunctive therapy that extends the recovery potential of the impaired limb.

Disclosures: **A.L. Kerr:** None. **E.M. Haan:** None. **R. Mavros:** None. **V. Nemchek:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.07/Z28

Topic: C.08.Stroke

Support: NIH R01-HD-065438

Title: Trade-off between efficacy and efficiency of motor training post-stroke

Authors: *N. SCHWEIGHOFER[1], C. WANG[1], C. J. WINSTEIN[2]
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Abstract: It is well known from motor learning research that motor performance depends on the amount of practice, but also that the gains follow diminishing returns: each additional unit of training yields smaller and smaller gains. Recent results from the DOSE trial, a single blind, phase I, randomized controlled trial of four doses (0, 15, 30, or 60 hours) of upper extremity therapy during the chronic phase after stroke, showed a robust dose-response relationship for the Motor Activity Log-Quality of Movement (MAL-QOM) (Winstein et al., in preparation). **Here,** we test the hypotheses that: 1) increasing the dose of training leads to an increase in the efficacy of training but a decrease in the efficiency of training, and 2) increasing the duration of training will also decrease the efficiency of training. We modeled the changes in the MAL during the train-wait-train-wait-train schedule used in the DOSE trial with novel dynamical mixed-effects models that account for individual response in changes in MAL both during and between training bouts. Using dose as input, we modeled the efficiency of training with dose; using time varying learning rates, we modeled the efficiency of training with duration; with the forgetting term, we modeled the decrease in MAL following training. Results confirmed the dose-response relationship previously found with regression models. The models also showed a decrease of efficiency with dose (the greater the doses, the less the gain per hour) and decrease in efficiency

with time (the longer the duration of training, the less the gain per hour). In addition, the greater the dose, the more the forgetting following training. However, the random learning and forgetting coefficients showed a large between subject variability in both increase and decrease in MAL as a function of dose and time. In conclusion, our novel model well accounted for the individual effects of motor training post-stroke and exhibited a trade-off between the gains due to training on one hand and the intensity and duration of motor training on the other hand.

Disclosures: N. Schweighofer: None. **C. Wang:** None. **C.J. Winstein:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.08/Z29

Topic: C.08.Stroke

Support: Startup funds from The Chinese University of Hong Kong

Title: Effects of a lower-limb exoskeleton on muscle synergies in healthy and chronic stroke patients

Authors: *L. RINALDI[1], L. YEUNG[2], P. LAM[1], M. PANG[3], R. TONG[2], V. CHEUNG[1]
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Abstract: According to muscle synergy hypothesis, movement's generation is achieved through a modular organization of the neuromuscular system, which is able to co-activate groups of muscles as single units, possibly thanks to the existence of spinal interneuronal structures. After a cerebrovascular accident, disruptions of the activation signals descending from the motor cortex may lead to abnormal muscle activation's patterns, with consequent motor impairment. Proper rehabilitation strategies are of crucial importance for motor recovery after a stroke event. The present work aims to study the effects induced by a new, actuated lower-limb exoskeleton on muscle activations during walking.
Healthy adults (N=5) and chronic stroke survivors (N=1) were asked to perform walking trials in 3 different experimental conditions: 1) natural walking, 2) walking wearing the inactive exoskeleton; 3) walking wearing the active exoskeleton. Electromyographic data (EMGs) of 14 lower limb and trunk muscles were recorded; the muscle synergies associated with each walking condition were extracted from filtered, rectified and normalized EMGs through Non-Negative Matrix Factorization Algorithm (NNMF). The similarity between synergy sets extracted from the three different conditions was assessed through their scalar products.

In healthy subjects, wearing the active or inactive exoskeleton did not alter the number of activated muscle synergies, when compared with natural walking; however, the exoskeleton was associated with changes in the muscular composition of >1 synergy, which involved muscles contributing to hip and pelvis stabilization. These motor adaptation strategies may be seen as a reactive balance response to the exoskeleton-induced external perturbations.
In the post-stroke patient, merging and fractionation of synergies were detected in the affected limb, when compared with the unaffected side's set. The activation of the exoskeleton reduced the number of muscles composing the merged synergies and was also associated with an increase in similarity between the synergies of the affected and unaffected-limb.
These findings suggest that the investigated exoskeleton does not interfere with the healthy natural muscle activations and motor adaptation strategies, and may stimulate effective neuromuscular responses in stroke survivors.

Disclosures: L. Rinaldi: None. **L. Yeung:** None. **P. Lam:** None. **M. Pang:** None. **R. Tong:** None. **V. Cheung:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.09/Z30

Topic: C.08.Stroke

Support: AHA Grant 10POST3200026

Title: Characteristics of sequential force development in stroke

Authors: *J. ROH[1,2], S. LEE[3,4], P. RAGHAVAN[5], W. Z. RYMER[6,2]
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Abstract: Previous studies suggest that activation of a small number of motor modules (i.e., coordinated patterns of muscle activity that flexibly combine to produce functional motor behaviors) underlies isometric force generation in stroke survivors and neurologically intact individuals. Our previous study demonstrated that stroke induces alterations in the composition of motor modules in the way that activation of some muscles is abnormally coupled. As we identified the 'post-stroke' alteration of modular organization of multi-directional force production during the stable force match phase, it remains unclear whether similar changes also

occur during the ‘dynamic’ phase of converging to solution (i.e., during force development). We thus examined whether stroke-specific motor module patterns also emerge over the exploratory course of isometric force matches. EMG was recorded from eight major muscles of the affected arm of eight chronic stroke survivors with severe impairment (Fugl-Meyer UE score < 25) and both arms of six age-matched control participants, during a 3-dimensional isometric force matching task. A non-negative matrix factorization algorithm identified motor modules in two time windows: exploratory force ramping phase, and stable force match. Correlation coefficients between any potential pair of end-point force components were also computed for the same time windows. Motor modules are conserved throughout the entire duration of isometric force development in both subject groups, as the same set of motor modules was identified during both phases of force generation. In stroke, the atypical co-activation of the three heads of the deltoid was conserved throughout force development. In both groups, all computed force correlations were significantly higher ($p < 0.05$) during the force ramping phase compared to stable force generation. In stroke, a higher force directional error was observed during the force ramp phase ($p < 0.05$). For both stroke and control groups, the CNS modulated the activation of the same set of motor modules to ramp up and stably maintain force, and the ‘abnormality’ in the composition of motor modules and their improper tuning appears to have contributed to the performance degradation post-stroke.

Disclosures: **J. Roh:** None. **S. Lee:** None. **P. Raghavan:** None. **W.Z. Rymer:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.10/Z31

Topic: C.08.Stroke

Support: 202346/Z/16/Z

Title: Motor cortex excitability in a simple reaction time task in post-stroke fatigue: Preliminary data

Authors: W. DE DONCKER[1], ***A. KUPPUSWAMY**[2], S. ONDOBAKA[1], *A. KUPPUSWAMY[2]
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Abstract: *Background:* Post-stroke fatigue is a debilitating, persistent symptom with significant impact on stroke survivors. We previously showed that post-stroke fatigue is associated with low levels of motor cortex excitability at rest. In this study we map the motor cortex excitability over time during the performance of a simple reaction time task and correlate excitability profile to

fatigue levels. The prediction is that those with high fatigue will show decreased excitability prior to movement. *Methods:* First time non-depressed stroke survivors, at least 3 months post-stroke, with minimal physical and cognitive impairment were recruited into the study. Fatigue levels were measured using the Fatigue Severity Scale - 7. Single pulse transcranial magnetic stimulation was used to measure excitability of the motor cortex as follows. Standard protocols as previously described was used to measure hotspot and threshold for eliciting a response in the affected side FDI. The intensity to obtain a 0.5 mV response in the affected side FDI was determined. The individual's reaction time was measured when the participant performed a ballistic finger abduction in response to an auditory 'go' cue. 70 trials of finger abduction were performed when TMS was delivered. Participants prepared to move when they heard the warning cue 500ms prior to the 'go' cue, which was the signal to perform a ballistic finger abduction. TMS was delivered at the warning cue, 333ms prior to 'go' cue, 167ms prior to 'go' cue, at the 'go' cue and 70% into the reaction time of the participant. Two more conditions, one where no warning cue was provided and other where no 'go' cue was provided. There were 10 trials in each condition delivered randomly. *Results:* We have currently tested 5 stroke survivors. Preliminary analysis show that stroke survivors with high levels of fatigue as measured by FSS-7 questionnaire have reduced excitability in the time leading up to the movement after presentation of the 'go' cue. Based on our previous results we proposed that post-stroke fatigue may be a disorder of sensorimotor control and less of a psychiatric problem. The data from our current study, thus far, lends support to this idea.

Disclosures: W. De Doncker: None. **S. Ondobaka:** None. **A. Kuppuswamy:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.11/Z32

Topic: C.08.Stroke

Title: Backward ArteriogeneSIS (BASIS) by mechanical barrier disruption and systemic erythropoietin pretreatment in mild and severe ischemic rat model

Authors: *G. PARK, E. CHOI, Y. KWON, K.-E. LEE, J. LEE, J. HONG
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Abstract: BACKGROUND: Stroke is one of the most disabled condition requiring restoration and revascularization is a promising strategy for the acute stroke. To achieve a successful backward arteriogenesis from healthy extracranial milieu, a simple combination therapy was performed with mechanical barrier disruption (MBD: skull and dura mater) and systemic erythropoietin pretreatment in rat model with cerebral perfusion impairment. **METHODS:** Mild

ischemia was assessed in male Sprague-Dawley rats (250 to 270g) with bilateral internal carotid artery ligation (bICAL). Severe ischemia was evaluated in male Wistar rats (230 to 250g) with bICAL and 90-min transient middle cerebral artery occlusion (tMCAO). Recombinant human EPO (5,000 U/kg) or saline was intraperitoneally injected for 3 consecutive days and then MBD was generated with a 2.5 mm burr-hole at the right side. In combination group and MBD-only group, we compared histology, vessel density, flow cytometry, gene expressions at different timeframes: acute for vasculogenesis (1 day and 4 days), subacute for angiogenesis (2 to 4 weeks), and chronic for arteriogenesis (4 to 12 weeks). **RESULTS**: (vs. hemisphere without MBD), hemisphere with MBD had microglial activation ($P < .05$) and upregulations of pro-inflammatory factors (*Tnf-α, Il-6, Il-1β,* $P < .001$) and Matrix metalloproteinase-9 (Mmp-9, $P < .01$) for increased vascular permeability, while EPO-combination group suppressed inflammatory responses (IBA-1, $P < .05$; *Tnf-α,* $P < .001$; *Il-6*, $P < .05$ vs. MBD-only group) and increased the prevalence of endothelial progenitor cells (EPCs) in acute period. Combination group had a successful transdural anastomosis with relative upregulations of proangiogenic factors in subacute period. Combination group also showed upregulation of proangiogenic factors (*Vegf*, $P < .001$; *Ang-2*, $P < .05$; *Vegfr-1*, $P < .05$) and increased vessel maturation (*Pdgf-β,* $P < .001$; *Tie-2*, $P < .05$) presenting the activation of MMP-2 ($P < .001$) in chronic period. Additionally, minocycline (blockade of MMPs) administration (45mg/kg, i.p.) decreased vascular maturation ($P < .05$) which is explained as the blockade of MMP-2 even in combination group ($P < .01$). Severe ischemic model with profound cerebral perfusion impairment showed more rapid backward arteriogenesis than mild ischemic model, which is presenting with the severity of cerebral perfusion as an environmental determinant for revascularization. **CONCLUSIONS:** Our data demonstrate that a combination method of MBD and systemic EPO pretreatment enhances vessel maturation without regression, which can be a promising therapeutic strategy for acute ischemic stroke victims.

Disclosures: G. Park: None. **E. Choi:** None. **Y. Kwon:** None. **K. Lee:** None. **J. Lee:** None. **J. Hong:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.12/AA1

Topic: C.08.Stroke

Title: 90 or over-year-old subarachnoid hemorrhage patients

Authors: *N. KUTSUNA[1,2], K. MAKITA[1,2], G. KIDO[1], Y. KAGAWA[1]
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Abstract: There will be more frequent incidence of clinical therapeutic judgement on 90 or over-year-old subarachnoid hemorrhage (SAH) patients while aging society has been expanding in the world. However, there are few evidence on therapeutic possibility for those patients. It is our purpose to report the possibility and features through consecutive 15 cases at two centers. Mean age was 91.5 ± 1.7 years old. World Federation of Neurological Surgeons grade on arrival was 3.5 ± 1.4 and average Fisher group was 3.8 ± 0.4. Mortality calculated from all patients was 66.7%. One case was suffered from symptomatic vasospasm. Five cases among all patients underwent surgical treatment including clipping or intervention. As a whole, Odds ratio was 0.0028 ($P < 0.05$, 95% confidence interval $0.0013 \leqq OR \leqq 0.5645$) in relation to survival between conservative therapy and surgery. The result supported surgical possibility for their longer life. However, mRS in all patients was very high at discharge, which indicated prevention of aneurysm rupture was important for them. As same as younger cases appropriate indication of surgery may be important for super-aged SAH patients despite of ruptured or unruptured aneurysm.

Disclosures: **N. Kutsuna:** None. **K. Makita:** None. **G. Kido:** None. **Y. Kagawa:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

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Topic: C.08.Stroke

Support: NIH Grant NS084069

NIH Grant NS099210

Title: Myoelectric computer interface training improves arm movement after stroke

Authors: *M. W. SLUTZKY[1], A. SINGH[2], S. HAMEED[2], E. M. MUGLER[1]
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Abstract: Impaired arm function after a stroke is due not only to weakness, sensory impairment, and spasticity, but also to abnormal co-activation patterns of arm muscles. We designed a paradigm that uses a myoelectric computer interface (MCI) to help stroke survivors reduce this abnormal co-activation. The MCI maps the activity of a pair of abnormally-coupled muscles to orthogonal components of cursor movement in a computer game, and the user learns to decouple

the muscles by moving the cursor to targets along the mapping directions. We evaluated the effects of in-laboratory training for over 18 sessions in 31 chronic stroke survivors. We compared the effects of training duration (60 vs. 90 minutes per session) as well as isometric vs. movement-based training conditions, for a total of 3 subject groups. We measured the degree of co-activation, arm joint kinematics, and clinical outcome metrics. All subject groups were able to reduce abnormal co-activation in targeted muscles using the MCI training. Each group showed a trend of reduced arm impairment after 6 weeks of training—Fugl-Meyer Assessment, improvement of 3.4±2.8 (mean±SE) for 60-min. group, 3.8±3.6 for 90-min. isometric group, and 3.5±3.4 for the 90-min. movement group). MCI training also appeared to improve subjects' arm function as measured by the Wolf Motor Function Test (-4.0 s, -7.8 s, and -6.9 s for the 60, 90, and isometric groups, respectively) and Motor Activity Log (3.9, 5.5, and 1.2 point gains for the 3 groups). Overall, there was a trend to improved function with longer training; no statistical difference was seen between movement-based and isometric training. Moreover, gains persisted at one month after training stopped. We are currently developing a wearable version of the MCI. We are testing the hypothesis that more frequent training, in the home setting, will translate to even greater gains in arm function. Subjects wear the electrodes home, play the MCI games daily using their abnormally co-activating muscles, and return to the lab weekly for testing. If successful, this paradigm could ultimately synergistically help patients undergoing more traditional rehabilitation, as well as those who have completed physiotherapy.

Disclosures: M.W. Slutzky: None. **A. Singh:** None. **S. Hameed:** None. **E.M. Mugler:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 674.14/AA3

Topic: C.08.Stroke

Title: Acute vagal nerve stimulation reduces infarct size but not motor impairment after stroke

Authors: K. OKADA[1], E. MARSCHALL[1], T. LITTLE[1], C. ROWAN[1], *J. A. KLEIM[2]
[1]SBHSE, [2]Sch. Of Biol. and Hlth. Systems Engin., Arizona State Univ., Tempe, AZ

Abstract: Stroke remains a major source of adult disability. More than 80% of stroke survivors will exhibit motor impairments and most will live with enduring deficits. Recent work has demonstrated that chronic vagal nerve stimulation (VNS) can enhance the efficacy of motor rehabilitation for reducing motor impairments. Here we examined whether VNS during the induction of cortical ischemia could alter both infarct size and post stroke motor impairment. Adult male rats were first trained to criterion on an automated isometric force task. Following training, animals were then assigned to one of three groups in a manner that counterbalanced pre-

stroke motor performance: Stroke, Stroke+VNS and Control. Animals in the Stroke condition received a cortical infarction via injections of endothelin 1 into the forelimb motor cortex contralateral to the trained limb. Animals in the Stroke+VNS group received the same cortical infarction in combination with thirty minutes of VNS and Control animals received neither a stroke nor VNS. Performance on the force task was then assessed for two weeks post stroke. Results showed that animals in the Stroke+VNS condition had significantly smaller cortical infarcts than animals in the Stroke condition. Both the Stroke and Stroke+VNS animals were significantly impaired on the force task compared to Controls for the entire two weeks of testing. Despite the differences in infarct volume, there were no differences in performance between the Stroke and Stroke +VNS animals. The results demonstrate that while acute VNS can reduce infarct volume, the protective effects do not translate to reductions in motor impairment. Current work is examining how cortical physiology may be altered during VNS.

Disclosures: K. Okada: None. **E. Marschall:** None. **T. Little:** None. **C. Rowan:** None. **J.A. Kleim:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

Location: Halls A-C

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Program#/Poster#: 674.15/AA4

Topic: C.08.Stroke

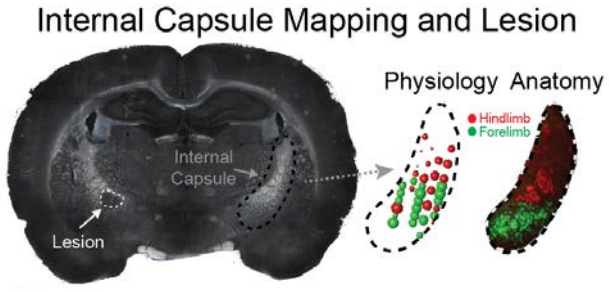
Support: R01NS092875

Title: A novel rat model of lacunar stroke targeting the forelimb area of the internal capsule

Authors: *A. SINDHURAKAR[1], V. C. RAMIREZ[1], T.-C. WEN[1], H. PARK[1], J. B. CARMEL[1,2]
[1]Burke Med. Res. Inst., White Plains, NY; [2]Neurol. and Pediatrics and Brain Mind Res., Weill Cornell Med., New York, NY

Abstract: Lacunar strokes of the internal capsule (IC) are common in people and often cause substantial and lasting motor impairments. Current rat models of IC stroke produce lesions that are inconsistent in their location and size. We describe the organization of the IC in the rat and a technique to specifically and reproducibly lesion the forelimb representation. We developed a 3-dimensional model of the rat IC that combines microstimulation mapping with anatomical tracing of axons from forelimb and hindlimb motor cortex. Both anatomy and physiology showed separate representations of the forelimb (Figure, green) and hindlimb (red) with a small overlap. We used an optrode (a sharp electrode and optical fiber) first to identify the forelimb representation using microstimulation and then, to lesion it. For the lesion, we systemically

injected Rose Bengal and delivered green light focally using a laser to activate the Rose Bengal only within the forelimb representation of IC. We found that the lesions were localized to forelimb area of the IC with minimal to no extension to adjacent areas, including the hindlimb region. Rats that underwent the procedure demonstrated significantly decreased forepaw movements contralateral to lesioned hemisphere compared with the non-targeted forepaw movements, as measured by the pasta manipulation task ($N=17$, $p<0.01$). The production of selective and reproducible lesion allows us to investigate changes in adjacent neural circuits. In sum, we can reproducibly achieve anatomically precise and behaviorally consistent changes that enable us to test hypotheses about how the corticospinal system adapts to lacunar stroke.



Disclosures: A. Sindhurakar: None. **V.C. Ramirez:** None. **T. Wen:** None. **H. Park:** None. **J.B. Carmel:** None.

Poster

674. Stroke: Non-Pharmacological Treatment and Activity-Dependent Plasticity and Recovery

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Program#/Poster#: 674.16/AA5

Topic: C.08.Stroke

Support: CIHR MOP 133568

Title: A cerebral artery stress test to assess regulation of cerebrovascular pulsatility during acute aerobic exercise in overt and covert stroke

Authors: *A. D. ROBERTSON[1], S. ATWI[2], K. KOSTOGLOU[3], R. XU[2], G. D. MITSIS[4], B. J. MACINTOSH[2]
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Abstract: Ischemic stroke and cerebral small vessel disease (CSVD) are associated with highly pulsatile cerebral hemodynamics. Whereas habitual exercise is believed to benefit neurovascular

health, acute exercise is a physiological stressor involving increased pulse pressure (PP). Healthy young adults protect the microcirculation from hypertensive injury during exercise through corresponding increases in cerebrovascular tone. Regulation of tone in older adults with vascular disease, however, is less characterized. This study examined pulsatile hemodynamics in relation to moderate intensity aerobic exercise in adults with cerebrovascular disease. Healthy young (n=17) and old adults (n=9), as well as old adults with CSVD (n=9) and chronic stroke (n=11), participated. We recorded arterial blood pressure and blood flow velocity through the middle cerebral arteries across resting (5 min), moderate intensity cycling (20 min), and recovery (5 min) phases. We used pulsatility index (PI) to characterize cerebrovascular hemodynamics, and critical closing pressure (CrCP) and resistance area product (RAP) to characterize regulatory mechanisms of cerebrovascular tone. Resting PP was greater in Stroke compared to Young (units - mm Hg; Young: 35±10; Old: 45±13; CSVD: 40±10; Stroke: 47±14; P=.035); whereas, we observed a non-significant group trend in baseline pulsatility index (PI) (units - ratio; Young: 0.89±0.12; Old: 0.92±0.16; CSVD: 0.93±0.15; Stroke: 1.06±0.23; P=.07). We did not observe group differences for the change in PI during exercise (P=.37). There were, however, group differences in the regulatory mechanisms underlying PI. Notably, group differences existed relating to the influence of RAP (P<.001) and CrCP (P<.001) on PI (Figure 1). These findings suggest hypertensive hemodynamic stresses during moderate intensity exercise do not present heightened risk for cerebrovascular patients. The mechanisms involved in regulating pulsatile hemodynamics, however, may vary with aging and cerebrovascular disease. Future non-linear time series analysis is warranted.

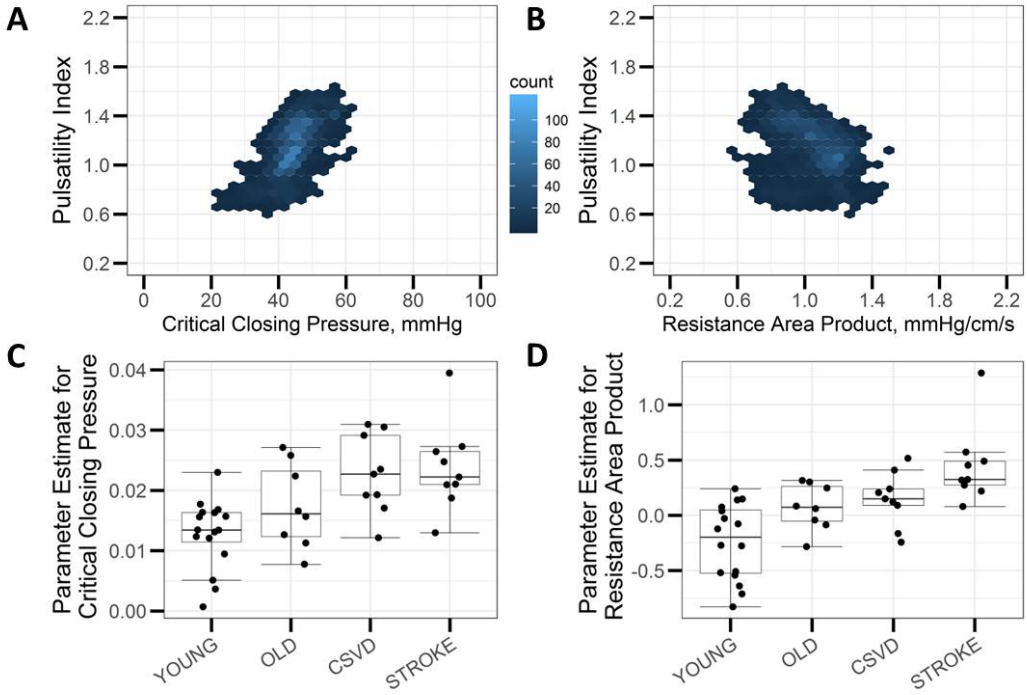

Figure 1. Scatterplots showing how middle cerebral artery pulsatility relates to critical closing pressure (A) and resistance area product (B) in a representative young participant. Group comparison of parameter estimates relating the independent effect of critical closing pressure (C) and resistance area product (D) on pulsatility index.

Disclosures: **A.D. Robertson:** None. **S. Atwi:** None. **K. Kostoglou:** None. **R. Xu:** None. **G.D. Mitsis:** None. **B.J. MacIntosh:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.01/AA6

Topic: C.09. Brain Injury and Trauma

Support: NSF STC CBET 0939511

NSF BRAIN EAGER DBI 1450962

Sengupta Start-Up

Title: Localized optogenetic stimulation and label-free imaging of neuronal cell activation

Authors: ***C. HU**, R. SAM, M. WANG, M. GILLETTE, P. SENGUPTA, G. POPESCU
Beckman Inst. for Advanced Sci. and Technol., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Imaging activation of cells typically requires exogenous fluorescent labels or sensors that change their properties when cells are activated. These sensors are either genetically encoded or delivered to the cells using a vehicle that that can pass through the plasma membrane. This process of labeling cells is often slow, tedious and inefficient. Additionally, it limits the reach of activity imaging in living cells as these sensors interfere with cellular pathways and are often toxic. In this study, we present a novel optical imaging system that enables label-free noncontact detection of neuronal cell activation induced by spatially-localized optogenetic stimulation of cells. We used transient transfection to express channelrhodopsin-2 (ChR2) in cells that enabled cell activation with a short pulse of blue light. We built a white-light Diffraction Phase Microscopy (wDPM) setup as an add-on module upon a commercial bright field microscope. By coupling a projector at the reflection port, this system allows spatially-resolved optical stimulation on specific cells in the field of view. For our experiments, we differentiated PC12 cells into neuronal lineage using nerve growth factor (NGF). Differentiated cells developed networks with neighboring cells when cultured in this fashion. We recorded wDPM videos from ChR2 transfected PC12 cell networks under three different conditions: no stimulation, blue (~460 nm) and red (~ 650 nm) light stimulation, in this order. For the control group, non-transfected networks were also subjected to the same stimulation conditions. Using the data outputted by our label-free method, we studied intracellular transport. Our experimental results indicate that ChR2 positive PC12 cell networks show enhanced mass transport after blue light stimulation, compared with red light stimulation, no stimulation and non-transfected cells.

To the best of our knowledge, this is the first demonstration of label-free imaging of cell activation with optogenetic stimulation.

Disclosures: **C. Hu:** None. **R. Sam:** None. **M. Wang:** None. **M. Gillette:** None. **P. Sengupta:** None. **G. Popescu:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.02/AA7

Topic: C.09. Brain Injury and Trauma

Support: CBP startup funding

Title: Murine cell and layer-specific distribution abnormalities in the hippocampus following trauma

Authors: ***Y. LEE**[1], M. E. KANDEL[2], S. JOUNG[3], I. UZCANGA[5], J. DE JESUS ASTACIO[6], C. BEST[4]
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Abstract: The hippocampus, a seahorse-shaped region of the brain, is responsible for emotions, learning, and memory. Compared to the rest of the brain, the hippocampus along with other mesial temporal structures is selectively vulnerable to Traumatic Brain Injury (TBI). This explains why memory impairment is one of the leading residual TBI-induced deficits and why forgetfulness is among the most frequent complaints heard from TBI patients and their relatives. The hippocampus has a characteristic anatomical organization comprised of multiple distinct areas and their respective layers, including the dentate gyrus (DG), Cornu Ammonis (CA3, CA2, CA1), subiculum (Sub), and entorhinal cortex (EC). Each region is composed of different cell types, distribution patterns and varied regional wiring. Here, we examine experimental trauma-induced hippocampal architectural alterations, and provide a detailed quantification of cellular and neurite morphology, fiber orientation, tomographic volumes and connectivity changes associated with trauma. The experimental trauma model is an adopted fluid percussion Instrument (Model FP301) injury model that supplies a reproducible impact. We visualize and quantify trauma-induced layer-specific and rostral to caudal structural shifts in stained and cleared *ex vivo*, and *in situ* hippocampi via light sheet microscopy (Carl zeiss Light sheet Z1 and Zen lite imaging software), and Spatial Light Interference Microscopy (SLIM) (Zeiss Axiovert, ImageJ and in-house software).

Disclosures: **Y. Lee:** None. **M.E. Kandel:** None. **S. Joung:** None. **I. Uzcanga:** None. **J. De Jesus Astacio:** None. **C. Best:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.03/AA8

Topic: C.09. Brain Injury and Trauma

Support: NSF CBET-0939511 STC

DBI 14−50962 EAGER

NSF IIP-1353368

Title: Neural structure and dynamics using halo-free phase-sensitive microscopy

Authors: ***G. POPESCU**[1], M. KANDEL[1], S. JOUNG[2], C. A. POPESCU[2]
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Abstract: Although phase contrast is extremely sensitive among transmitted light modalities, features of interest such as neurons near cell bodies are often obscured by a strong “halo” artifact, perturbing quantitative analysis. Recent advances in modeling image formation in common-path interferometers have shown that this artifact is due to the coherent addition of many waves at the image plane - and the halo effect arises due to the limited spatial coherence of the illumination. Thus, microscope manufacturers face an unfortunate trade-off between high detail (incoherent) and low detail (coherent) optimized systems. In this work, we propose a method to break this dichotomy, by carefully mixing corrupt low-frequency data corresponding to the outline of the cell with high-fidelity intracellular details in a way that completely preserves the quantitative nature of the high-frequency content. Specifically, we propose a digital filtering technique for quantitative phase images that is deterministic, requires no manual interaction or point spread function measurements and operates at video rates. To validate our technique we study the time evolution of adherent neuron cultures whose neurites were obscured by the halo artifact.

Disclosures: **G. Popescu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PhiOptics Inc. **M. Kandel:** None. **S. Joung:** None. **C.A. Popescu:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

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Program#/Poster#: 675.04/AA9

Topic: C.09. Brain Injury and Trauma

Support: CBP Startup Funds

Title: Using spatial light interference microscopy (SLIM) to quantify the neuroprotective effects of temperature and docosahexaenoic acid (DHA) on primary neurons following trauma

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Abstract: Traumatic Brain Injury (TBI) may cause severe neuronal damage, alterations in cerebral blood flow and metabolism, and ultimately consequent long-term cognitive and memory deficits, disturbances in mood and behavior, as well as impairments in motor coordination. Thus, TBI represents an important healthcare concern with an estimated 5.3 Million Americans living with a TBI-related disability. Additionally, TBI is a contributing factor in a third (30.5%) of all injury-related deaths in the United States. Despite more than 50 clinical trials, and at least 30 proposed pharmacological compounds, there have been few advances in TBI patient management over the last twenty years. Here, we study two therapeutic approaches, *Docosahexaenoic Acid* (*DHA*, 25 μM and 50 μM) treatment and *Therapeutic Hypothermia* (TH, 24^0C, 34^0C, and 37^0C), and we investigate their relative effectiveness as neuroprotectants in a neuronal cell trauma model of TBI. DHA treatment and TH are thought to limit and prevent the secondary pathological effects of TBI following the initial acute stage neural trauma caused by the mechanical forces of impact. The mechanisms of action of both DHA and TH include the regulation of physicochemical properties such as neural membrane fluidity, permeability and viscosity in synaptic membranes; the modulation of neurotransmission, gene expression, and activities of enzymes, receptors and ion channels. These processes are closely associated with activation of signaling pathways that sustain synaptic function and neuronal survival via limiting oxidative stress, inflammation and apoptosis. Using a standard cell survival assay, trypan blue, and in combination with a novel quantitative form of microscopy Spatial Light Interference Microscopy (SLIM), Dispersion-Relation Spectroscopy, a cell trauma device (AMScien Instruments), an Arduino based temperature regulator, and *in vitro* murine neuronal cell cultures, we characterize and quantify DHA and TH-induced changes in cell survival, neuronal structural integrity (neurite length and width, and number of branch points), membrane dynamics (transport

rates) after cell culture exposure to mechanical impact (2.5 and 5atm). We show that *DHA* (25 μM) and TH (24^0C, 34^0C) impart significant neuroprotection in our cell trauma model.

Disclosures: I. Miches: None. **P. Cintora:** None. **Y.J. Lee:** None. **M.E. Kandel:** None. **D. Kline:** None. **C.A. Best-Popescu:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

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Program#/Poster#: 675.05/AA10

Topic: C.09. Brain Injury and Trauma

Support: NSF DBI 1450962 BRAIN EAGER

NSF STC CBET 0939511

Title: Gradient light interference microscopy (GLIM) for label-free imaging of acute brain slices

Authors: *M. E. KANDEL[1], G. N. KOUZEHGARANI[2], M. U. GILLETTE[2], G. POPESCU[1]
[1]Electrical and Computer Engin., Univ. of Illinois At Urbana-Champaign, Champaign, IL; [2]Dept. of Cell & Developmental Biol., Univ. of Illinois, Urbana, IL

Abstract: Turbid structures such as acute brain slices are difficult to image with visible light, as incoherent contributions from out of focus planes obscure the sample. To improve the contrast of a conventional patch clamp setup, we construct an add-on module capable of introducing four controlled phase shifts between the laterally sheared beams in DIC. Our interferometer, referred to as GLIM, enables us to record phase maps, which implicitly cancel background contributions from out of focus planes. The resulting phase map is a relief style image that can be used to assay quantitative microscopy parameters such as mass transport or cell growth. GLIM is presented as a fully automated add-on to a conventional DIC microscope performing the interferometric reconstruction at video rates. Here we show our early work on characterizing the transport phenomena in acute brain slices over comparably long periods of times that would be otherwise difficult to achieve using conventional techniques.

Disclosures: M.E. Kandel: None. **G.N. Kouzehgarani:** None. **M.U. Gillette:** None. **G. Popescu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Phi Optics Inc..

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

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Program#/Poster#: 675.06/AA11

Topic: C.09. Brain Injury and Trauma

Support: Neuroscience program, Central Michigan University

College of Medicine, Central Michigan University

Chemistry and Biochemistry, Central Michigan University

Field Neurosciences Institute

John G. Kulhavi Professorship

Title: Introduction of pamam dendrimers to glioma and glioblastoma cell cultures induces severe effects and significantly reduced cell viability

Authors: *M. FINI[1], B. SRINAGESHWAR[6], A. N. STEWART[2], D. SWANSON[3], G. L. DUNBAR[4], A. SHARMA[5], J. ROSSIGNOL[7]
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Abstract: Glioblastoma Multiforme (GBM) is a common and hyper aggressive brain cancer which has a median survival time of 12 to 15 months after diagnosis. Typical treatment includes partial resection, followed by a combination of radiotherapy and chemotherapy in an attempt to kill the remaining cancerous cells. A primary characterization of this tumor is a high inflammatory response that is aided by a hypoxic environment the growing tumor creates. In combination with this high inflammatory response, the tumor's aggressive, expansive, and random nature, it extremely unlikely to eradicate the whole tumor. The aim of this study is to examine the effects that a newly emerged family of synthetic carbon nanoparticles, known as dendrimers, has on the Glioma 261 mouse and F98 rat cell line *in vitro.* Mesenchymal stem cells, neuronal stem cells and primary cortical neurons derived from mouse were used as control cells to also observe the particles effects on non-cancerous cells. Confocal images were also taken of these cell lines to observe the pattern and distribution of the dendrimer after it is taken up. These dendrimers, which are 3-dimentional and can have different surface groups, have exhibited many unique properties, such as anti-inflammatory properties. To be able to thoroughly study the effects of the dendrimer, we used a modified fourth generation that was comprised of 90% OH

(neutral) groups and 10% NH_2 (cationic) groups, which is approximately 4nm in diameter. Two compositions of the same dendrimer were used in two different experiments; the first composition of dendrimer with the FITC fluorescent marker attached to the NH_2 groups, while the other composition lacked the FITC marker. The first experiment conducted was to introduce the two compositions of dendrimers into a cell culture of the respective cells to observe the effects it has on cell proliferation and adhesion. The second experiment was administering an MTT assay on the two cancer cell lines and the control cell lines previously listed to assess the mitochondrial metabolism and if the effects were significant enough to reduce the viability of the cells. The findings showed that both compositions had negative effects on the cells while in culture, and showed a significant reduction of tumor cell viability in the MTT assay.

Disclosures: M. Fini: None. **B. Srinageshwar:** None. **A.N. Stewart:** None. **D. Swanson:** None. **G.L. Dunbar:** None. **A. Sharma:** None. **J. Rossignol:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.07/AA12

Topic: C.09. Brain Injury and Trauma

Support: CNRS

ANR/Labex/Cortex

ANR/parietalmapping

Title: Restoring large scale brain activity and consciousness with vagus nerve stimulation

Authors: *A. SIRIGU[1], M. CORAZZOL[1], G. LIO[1], A. LEFEVRE[1,2], N. ANDRÉ-OBADIA[2], P. BOURDILLON[2], J. LUAUTE[2], M. GUENOT[2]
[1]Inst. of Cognitive Sci. Marc Jeannerod, BRON Cedex, France; [2]Hospices Civils de Lyon, Lyon, France

Abstract: Vegetative state is a severe disorder of consciousness characterized by a disruption in thalamo-cortical ascending pathway and fronto-parietal functions. We hypothesized that stimulation of the vagus nerve a neural pathway which provides bodily inputs to the brain and is widely distributed throughout the CNS, promotes the return of consciousness. We investigated the effects of chronic VNS in a patient in a vegetative state since 15 years. Within four weeks after VNS, the patient's ability to respond to and follow external stimulation increased and his state transitioned from vegetative to minimally conscious as assessed by standard coma tests. Importantly, VNS induced improvements in consciousness were correlated to several brain measures of sub-cortical and cortical activity. A significant increase of information sharing, a

measure previously identified as a sensitive index of consciousness, was observed after VNS over a parietal region within a cluster including the right centrotemporooccipital electrodes. Interestingly, this improvement in cortical communication overlapped within regions previously identified as hot zones for consciousness. Our study demonstrates the therapeutic potential of VNS to modulate large-scale human brain activity and alleviate disorders of consciousness.

Disclosures: **A. Sirigu:** None. **M. Corazzol:** None. **G. Lio:** None. **A. Lefevre:** None. **N. André-Obadia:** None. **P. Bourdillon:** None. **J. Luaute:** None. **M. Guenot:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.08/AA13

Topic: C.09. Brain Injury and Trauma

Title: Repeat concussive TBI and prevention by paclitaxel is characterized by imaging biomarkers with pathologic confirmation in mice

Authors: *C. G. CROSS[1], J. S. MEABON[2], M. M. CLINE[2], M. A. OSTLIE[1], D. G. COOK[2], D. J. CROSS[1], S. MINOSHIMA[1]
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Abstract: Introduction
We previously showed that intranasal paclitaxel (PTX) was neuroprotective for cognitive deficits in repeat concussive brain injury (rcTBI). PET and MR imaging have been proposed as biomarkers to evaluate rcTBI clinically. In this study, we hypothesized that imaging could be used in mice to characterize rcTBI as well as response to therapeutic intervention by paclitaxel.
Methods
Intranasal PTX (0.6 mg/kg; n=6) or saline (SAL) (n=9) was administered only after the first repeat concussive controlled cortical impact (rcCCI) in a series of one impact/day for five days (n=15) or sham rcCCI (n=8). Diffusion tensor imaging (DTI), T1-weighted (T1W) and T2-maps were acquired on 14T high res MR scanner at 9 days post rcCCI. Fractional anisotropy (FA) was compared using manual ROIs as well as FSL tract-based spatial statistics (TBSS). Glucose metabolism was assed via SUV corrected 18F-flurodeoxyglucose (FDG) PET imaging as a biomarker for synaptic activity at 35 days. At 45 days, brains were evaluated for pathologic evidence of axonal injury (silver stain) and synaptic loss (PSD-95) in the external capsule and hippocampus respectively.
Results
FA in the external capsule was decreased in SAL-rcCCI by 17% compared to SHAM (0.21±0.01 vs 0.25±0.01, $p \leq 0.05$) and extensive areas of white matter injury were seen by TBSS. However, PTX-rcCCI was not significantly different from SHAM or SAL-rcCCI with either analysis. With

silver stain, axonal degeneration was seen in cortical white matter of the external capsule in 5/6 SAL-rcCCI but not PTX-treated (n=0/5). A single, dystrophic axon was observed in 1/8 shams. T1W and T2 images revealed focal abnormalities in the cortex below area of repeat impact in all SAL-rcCCI mice that were not apparent in PTX-rcCCI. SAL-rcCCI showed significantly decreased brain FDG uptake, which was "normalized" in PTX mice. Whole brain SUVs, were 120.5±30.1, 90.3±18.7 and 129.2±23.0, for SHAM, SAL- and PTX-rcCCI respectively, $p \leq 0.05$. In SAL-rcCCI, hippocampal PSD-95 immunofluorescence was reduced compared to both SHAM and PTX.

Conclusion

Paclitaxel prevented alterations in white matter structure and glucose metabolism from rcCCI that were detected by both MRI and PET imaging modalities. However, only FDG-PET confirmed that PTX resulted in improvement when pathology indicated both synaptic loss AND axonal injury were prevented with PTX. DTI may not be sensitive enough or may have more inherent variability to detect treatment-related benefit in rcTBI. Further research is needed to distinguish these factors.

Disclosures: C.G. Cross: None. **J.S. Meabon:** None. **M.M. Cline:** None. **M.A. Ostlie:** None. **D.G. Cook:** None. **D.J. Cross:** None. **S. Minoshima:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

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Program#/Poster#: 675.09/AA14

Topic: C.09. Brain Injury and Trauma

Support: International Rett Syndrome Foundation Grant 3216

International Rett Syndrome Foundation Grant 3206

Title: IGF-1 and behavioral training as potential therapeutic strategies to improve behavioral deficits in a rat model of Rett syndrome

Authors: *K. ADCOCK[1,3], A. BERRY[3], J. RILEY[1,3], A. ALVAREZ-DIEPPA[1], J. BUCKSOT[2,3], R. HERD[3], R. L. RENNAKER[2,3], C. ENGINEER[3], S. A. HAYS[2,3], M. P. KILGARD[1,3]

[1]Behavioral and Brain Sci., [2]Bioengineering, Univ. of Texas at Dallas, Richardson, TX; [3]Texas Biomed. Device Ctr., Richardson, TX

Abstract: Rett syndrome is a rare neurological disorder associated with a mutation in the X-linked gene MECP2. This disorder mostly affects females, who typically have normal early development followed by a regression of skills. The recently developed MeCP2 transgenic rat

model exhibits symptoms commonly observed in of Rett syndrome patients, including seizures, breathing abnormalities, motor abnormalities, anxiety, and communication deficits. Extensive behavioral therapy can improve language, cognitive, and social functioning for individuals with autism. More recently, behavioral training in Rett Syndrome patients also provided improvements in cognitive performance. Insulin-like growth factor 1 (IGF-1) therapy has also been successfully utilized in both human clinical trials and in rodent models, with improvements in apnea, anxiety, and restoration of plasticity deficits. We first sought to characterize the ability of MeCP2 heterozygous (Het) rats to perform a complex speech discrimination task and a skilled motor task. Mecp2 and WT rats were trained to discriminate human speech sounds (i.e., /dad/ v. /bad/) in quiet and in various levels of background noise. Additionally, rats were also trained on a skilled lever press task to evaluate motor learning. Preliminary data indicates behavioral impairments in both the perceptual and motor tasks. As expected, MeCP2 rats also exhibit atypical social and anxiety behaviors compared to WT littermates.
Ongoing experiments are directed at investigating whether behavioral therapy and/or IGF-1 therapy can improve the observed deficits in perceptual, motor, and cognitive function. These studies may lead to the development of novel therapies to improve the quality of life of Rett syndrome patients.

Disclosures: K. Adcock: None. **A. Berry:** None. **J. Riley:** None. **A. Alvarez-Dieppa:** None. **J. Bucksot:** None. **R. Herd:** None. **R.L. Rennaker:** None. **C. Engineer:** None. **S.A. Hays:** None. **M.P. Kilgard:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

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Program#/Poster#: 675.10/AA15

Topic: C.09. Brain Injury and Trauma

Support: NIMH MH 086960-01A1

DARPA ElectRx

Title: Mechanisms of VNS-induced extinction enhancement and PTSD symptom reduction in rats

Authors: *L. J. NOBLE[1], J. E. CHILDS[2], A. V. CHUAH[2], V. B. MERUVA[2], S. KROENER[3], C. K. MCINTYRE[4]
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Abstract: Posttraumatic stress disorder (PTSD) can develop following a traumatic event. Symptoms of PTSD include hypervigilance, avoidance, and increased anxiety. Exposure therapy is a form of cognitive behavioral therapy that is commonly used to treat these symptoms. During exposure therapy, patients are repeatedly exposed to cues that remind them of the trauma until they learn healthier responses to those cues. However, PTSD patients show impairments in extinction learning, which may increase dropout and nonresponse rates. Adjuncts to exposure therapy could be utilized to enhance its effectiveness by promoting successful extinction learning and accelerating the course of treatment. Vagus nerve stimulation (VNS) is an FDA-approved treatment for the prevention of seizures. VNS shows promise as an adjunct for exposure therapy because it enhances memory consolidation in rats and in humans, and we recently found that pairing VNS with unreinforced exposures to a conditioned stimulus enhanced extinction learning and protected against relapse in the extinction-resistant single prolonged stress (SPS) rat model of PTSD. Furthermore, we found that administration of VNS during extinction led to subsequent elimination of PTSD-like symptoms one week later. These results indicate that extinction impairments contribute to general symptoms of PTSD and, therefore, treatments that promote successful extinction should produce benefits that reach beyond the cue-induced fear. Alternatively, VNS may generally reduce symptoms of fear, arousal, and anxiety. The current studies are designed to examine the mechanisms by which VNS enhances extinction of conditioned fear, and reduces PTSD-like symptoms in rats subjected to SPS. Unpaired administration of VNS in the homecage prior to elevated plus maze testing increased time spent in open arms, and this effect was attenuated by peripheral administration of methylscopolamine, a muscarinic antagonist that does not cross the blood brain barrier, indicating that VNS alone produces an anxiolytic effect that depends on peripheral parasympathetic effects. However, methylscopolamine did not interfere with VNS enhancement of extinction. These results indicate that VNS-induced extinction enhancement does not depend on peripheral vagal activation. Rats subjected to SPS show alterations in synaptic plasticity in the pathway from the medial prefrontal cortex to the basolateral complex of the amygdala. Current studies are aimed at elucidating the mechanisms by which VNS acts within the central nervous system to enhance extinction and alleviate PTSD-like symptoms in rats.

Disclosures: L.J. Noble: None. **J.E. Childs:** None. **A.V. Chuah:** None. **V.B. Meruva:** None. **S. Kroener:** None. **C.K. McIntyre:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.11/AA16

Topic: C.09. Brain Injury and Trauma

Title: Pairing vagus nerve stimulation with motor training to enhance motor recovery after stroke: Effects of parametric variations of stimulation intensity

Authors: *D. PRUITT[1], ***D. PRUITT**[1], T. DANAPHONGSE[2], M. LUTCHMAN[2], R. L. RENNAKER[2], M. P. KILGARD[2], S. A. HAYS[2]
[1]Univ. of Texas at Dallas, Richardson, TX; [2]Texas Biomed. Device Ctr., The Univ. of Texas at Dallas, Richardson, TX

Abstract: Stroke is a leading cause of long-term disability. Currently, there are no effective rehabilitative therapies for chronic stroke patients. Previously, we have determined that pairing vagus nerve stimulation (VNS) with motor training enhances recovery of motor function is multiple models of stroke. VNS provides a new therapeutic avenue to treat patients suffering from a stroke, but it is necessary to investigate what stimulation parameters provide the optimal benefit. In this study, we tested multiple intensities of VNS paired with motor training to determine the stimulation intensity that is most effective at enhancing functional recovery. We trained animals on a supination task. After proficient at the task, animals received an ischemic stroke with endothelin-1 (ET-1). Animals then continued motor training while receiving VNS at an intensity of 0.4 mA, 0.8 mA, 1.6 mA, or no VNS at all. We found that VNS was successful at enhancing motor recovery, and we expand upon the effects of each stimulation intensity on motor recovery.

Disclosures: D. Pruitt: None. **T. Danaphongse:** None. **M. Lutchman:** None. **R.L. Rennaker:** None. **M.P. Kilgard:** None. **S.A. Hays:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.12/AA17

Topic: C.09. Brain Injury and Trauma

Title: Optimizing vagus nerve stimulation paired with rehabilitation to enhance recovery following spinal cord injury

Authors: ***M. DARROW**[1,5], A. D. RUIZ[2], P. D. GANZER[3], L. BARRON[6], A. BERRY[6], M. BILAL[6], R. L. RENNAKER[7], M. P. KILGARD[4], S. A. HAYS[3]
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Abstract: There are approximately 17,000 cases of spinal cord injury (SCI) each year in the United States. Despite extensive rehabilitation, most patients are left with chronic impairments in motor function. Therapeutic interventions to improve recovery of function after SCI are needed. Recent evidence suggests that repeatedly pairing vagus nerve stimulation (VNS) with rehabilitation can drive plasticity in motor circuitry in the central nervous system and enhance forelimb recovery in models of neurological injury and disease. However, little is known about the optimal delivery strategy for this potential therapy. We evaluated the capacity of four distinct VNS delivery paradigms to enhance motor recovery in a model of SCI. Rats were trained on the isometric pull task, an automated, quantitative measure of forelimb strength. Animals received a right side cervical spinal contusion at level C5/C6 to impair function of the trained forelimb. Starting on the sixth week post-injury, animals were assigned to balanced treatment groups to receive either rehabilitative training without stimulation (Rehab), equivalent rehabilitative training in which VNS was paired with forelimb movement on trials with the strongest sixth of pull forces(VNS + 17% Best Rehab), equivalent rehabilitative training in which VNS was paired with forelimb movement on every trial independent of pull force (VNS + 100% Rehab), equivalent rehabilitative training in which VNS was paired with forelimb movement on trials with the weakest sixth of pull forces(VNS + 17% Worst Rehab), or equivalent rehabilitative training in which VNS was paired with forelimb movement on trials with the strongest sixth of pull forces but delayed 2 seconds (VNS + 17% Best Rehab Delayed). Forelimb function was evaluated over the course of six weeks of rehabilitative training. Rats were then placed in their home cage and returned for an additional week of behavioral testing four weeks later to allow assessment of lasting effects. At the completion of forelimb testing, all animals underwent intracortical microstimulation motor mapping. The VNS + 17% Best Rehab, VNS + 100% Rehab, and VNS + 17% Best Rehab Delayed paradigms improve motor recovery beyond rehabilitation alone. Also, VNS + 17% Worst Rehab is not better than Rehab and is significantly worse than the other groups receiving VNS. Preliminary ICMS data indicates that enhanced plasticity in motor cortex is associated with improved recovery of function. Consistent with our previous studies, VNS delivered during rehabilitation enhances motor recovery after SCI. Ongoing studies are directed at evaluating the stability and generalizability of VNS-dependent benefits.

Disclosures: M. Darrow: None. **A.D. Ruiz:** None. **P.D. Ganzer:** None. **L. Barron:** None. **A. Berry:** None. **M. Bilal:** None. **R.L. Rennaker:** None. **M.P. Kilgard:** None. **S.A. Hays:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.13/AA18

Topic: C.09. Brain Injury and Trauma

Title: Vagus nerve stimulation enhances plasticity and improves recovery following peripheral nerve injury

Authors: *E. MEYERS[1,4], B. R. SOLORZANO[4], R. GRANJA-VAZQUEZ[5], P. D. GANZER[2,4], M. DARROW[1,4], M. I. ROMERO-ORTEGA[6], R. L. RENNAKER[7,4], M. P. KILGARD[3,4], S. A. HAYS[2,4]
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Abstract: Long-term impairment of hand function is a common consequence following peripheral nerve injury. Insufficient plasticity in central networks has been implicated in poor recovery. Here we tested the hypothesis that enhancing central plasticity could improve recovery after forelimb nerve injury. We utilized a targeted plasticity therapy consisting of short bursts of vagus nerve stimulation (VNS) paired with rehabilitative training following median and ulnar nerve transection and repair. Subjects receiving VNS paired with rehabilitation displayed significantly increased forelimb strength and improved mechanosensation compared to subjects receiving a matched amount of rehabilitative training without VNS. Physiological and anatomical studies revealed that pairing VNS with rehabilitation increased functional connectivity in descending motor networks. Furthermore, a matched amount of VNS delivered after daily rehabilitation sessions failed to improve recovery or enhance plasticity. VNS did not affect the morphology of the injured nerves suggesting that peripheral nerve changes did not mediate recovery. Finally, disrupting the cortical cholinergic system blocked the plasticity enhancing effects and the improved recovery observed in paired VNS subjects. Together, these findings highlight the importance of plasticity in recovery after peripheral nerve injury and suggest that strategies to enhance plasticity may provide an additional avenue to improve sensory and motor recovery.

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Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.14/AA19

Topic: C.09. Brain Injury and Trauma

Support: Adelson Foundation

Title: Identification of axon growth promoting small molecules using a high throughput phenotypic assay exploiting hiPSC derived human sensory, motor and cortical neurons

Authors: *B. SINGH, T. HO, Y.-C. CHENG, J. MERCIER, C. J. WOOLF
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Abstract: Central nervous system (CNS) injuries are debilitating and lead to permanent disability because of the limited growth of axons after injury, attributable both to a lack of an intrinsic growth capacity and presence of extrinsic growth inhibitory cues. Previous preclinical screens for compounds to promote axonal growth in the CNS using heterologous expression systems have not translated to the clinic because the assay does not recapitulate the natural molecular architecture of neurons or their post-translational state. Similarly, mouse primary neurons are difficult to generate in sufficient numbers for high throughput screening (HTS) and they have large variances in axonal growth, making screening problematic (low Z').
We have generated standardized protocols to differentiate sensory, motor and cortical neurons from hiPSCs and also have developed a robust, sensitive and reproducible phenotypic neurite outgrowth assay (Z'>0.5) that recapitulate PNS and CNS specific growth phenotypes *in vitro.* This provides us with a means to screen for regeneration-promoting compounds in a high throughput mode. We are currently screening a diverse annotated bioactive compound libraries (>3,000 compounds) for neurite outgrowth promotion in human sensory, motor and cortical neurons on permissive (laminin) and inhibitory (CSPG and myelin) substrates. Neurite outgrowth and neuronal survival is measured using the Thermo Cellomics Arrayscan XTI following exposure to test compounds. We have achieved a Z'>0.5 using Y-27632 (Rock inhibitor) for cortical neurons on myelin and BDNF for sensory neurons on laminin, as positive controls. Positive hits will be classified as any compound that results in neurite outgrowth levels significantly higher than DMSO controls ($p<0.05$). Once we identify hits, we will execute target identification by deconvolution, and then target validation using CRISPR KO or overexpression, as the first stage towards identifying targets suitable for developing novel therapeutics to treat CNS and PNS injuries.
We will identify targets involved in promoting growth of CNS neurons in an inhibitory environment and growth of PNS neurons in a permissive environment. These will represent the foundation for further studies; test activity in primary rodent neurons and in models of spinal cord and peripheral nerve injury; conduct target based HTS. The combination of stem cell technology enabling differentiation of defined human neurons combined with high content screening capacity offers an opportunity for a transformative change in regeneration target identification - one that is both unbiased and human focused. This work is supported by Adelson foundation.

Disclosures: B. Singh: None. **T. Ho:** None. **Y. Cheng:** None. **J. Mercier:** None. **C.J. Woolf:** None.

Poster

675. Traumatic Brain Injury: Therapeutic Interventions III

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 675.15/AA20

Topic: B.09. Physiological Properties of Neurons

Support: R01NS072171

Title: Multimodal treatment using transcranial magnetic stimulation and environmental enrichment improves motor and sensory function after TBI

Authors: *S. SHIN[1], V. S. KRISHNAN[2], W. STOKES[3], H. LU[3], P. LU[3], G. PELLED[4]
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Abstract: Traumatic brain injury (TBI) is a leading cause of death and disability. The majority of therapeutic strategies has failed in clinical trials and was attributed to the heterogeneous pathophysiology. Recently, multimodality treatments have been considered to be an area of promising future endeavors. Transcranial magnetic stimulation (TMS) has been shown as a promising noninvasive therapeutic intervention for neuropathological diseases, stroke, as well as TBI (Lu H et al., 2015; Shin SS and Pelled G, 2017). Nevertheless, we demonstrated that pairing TMS with another mode of stimulation may augment its long-lasting effect (Banerjee et al., 2017). Since environmental enrichment (EE) was shown to improve motor and memory function, we tested if TMS paired with EE will facilitate recovery to a greater degree compared to each of the modalities alone. We subjected rats to controlled cortical impact, and then assigned them to one of the four groups: 1. no further treatments (TBI), 2. environmental enrichment after injury (TBI-EE), 3. TMS for 1 week after injury (TBI-TMS), and 4. TMS and environmental enrichment (TBI-TMS-EE). Rats receiving EE were housed in a communal cage with various stimuli such as toys and ladders. The TMS group had 10Hz repetitive TMS over 7 days. Functional outcomes were assessed at short term (7 days) and long term (6 weeks) by a battery of sensory and motor tests: primary somatosensory cortex local field potential (LFP), bicep motor evoked potential (MEP) assessed by electromyography, and beam walk test as well as challenge ladder test. At short term, TBI-TMS and TBI-TMS-EE groups had significantly LFP amplitudes compared to TBI and TBI-EE groups ($P<0.05$). Additionally, TBI-TMS-EE group had significantly improved performance on beam walk test compared to TBI group ($P<0.001$). However, no differences were detected by MEP. To investigate the long term effect of multimodality treatment, TBI-TMS-EE group was compared to TBI-TMS group at 6 weeks. There was significantly improved performance in challenge ladder by the TBI-TMS-EE group compared to TBI-TMS group ($P<0.01$). Additionally, there was higher somatosensory cortex

LFP amplitude (P<0.05) as well as MEP (P<0.05) in TBI-TMS-EE group compared to TBI-TMS group. When the rats from both groups were compared using evoked-functional MRI (fMRI) to a forepaw stimulation, TBI-TMS-EE group had higher number of activated pixels (P<0.01). This study explored the idea of combining a noninvasive magnetic stimulation with rehabilitative training in an EE. We demonstrate here for the first time that combined therapy using TMS and EE enhances both motor and sensory function following TBI compared to TMS or EE alone.

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Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.01/AA21

Topic: C.09. Brain Injury and Trauma

Support: CIHR

Canadian Diabetes Association

Alberta Diabetes Institute

Title: Novel non-viral knockdown strategies targeting retinoblastoma protein for rescue and regeneration of peripheral axons

Authors: *K. ZUBKOW[1], T. M. POITRAS[1], A. CHANDRASEKHAR[1], D. W. ZOCHODNE[2]
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Abstract: Retinoblastoma protein (Rb1) is a tumor suppressor protein that acts as a cell cycle inhibitor through its interaction with the transcription factor E2F. In previous work (Christie, Krishan et al., Nat Commun, 2014), we identified its expression in peripheral sensory neurons and the impact of its knockdown on regeneration. In the adult peripheral nervous system, tumor suppressor proteins such as Rb1 hinder neuroplasticity, a disadvantage when regeneration and rescue of neurons and axons is critical. Here we addressed whether two novel strategies for non-viral siRNA delivery in two differing models of peripheral nerve damage had the ability to enhance recovery. In the first paradigm, we assessed whether delayed local Rb1 siRNA delivery to the hindpaw using an electroporation protocol might confer pro-regeneration benefits following a nerve crush injury. The protocol was associated with robust knockdown of Rb1 in ipsilateral dorsal root ganglia (DRG) sensory neurons, indicating an impact of the siRNA through retrograde transport. The second model was a chronic model of diabetic neuropathy induced by streptozotocin injection and persistent hyperglycemia over 3 months. Rb1 was knocked down in lumbar DRGs by intranasal administration. Both studies used male CD1 mice,

mechanical and thermal sensory testing, and electrophysiological testing. Two weeks after sciatic nerve crush, mice received a total of 8 hindpaw injections with local electroporation of either Rb1 or control scrambled sequence siRNAs over 2 weeks. 28 days following injury, motor conduction velocities in Rb1 siRNA-treated mice, but not controls given scrambled siRNA, showed recovery to pre-injury levels indicating more rapid maturation of regenerating myelinated motor axons. There was also preliminary evidence of greater recovery of thermal and mechanical sensation in mice given Rb1 siRNA. In diabetic mice with neuropathy, those treated with Rb1-targeted siRNA had higher motor and sensory conduction velocities at endpoint, comparable to values in non-diabetics. Rb1, but not scrambled, siRNA appeared to restore thermal sensitivity to baseline levels. Suppression of Rb1 may enhance plasticity and functional recovery of thermal sensitivity and nerve conduction velocity in models of peripheral nerve damage. While our preliminary findings require additional investigation, we note that novel forms of siRNA delivery may offer important benefits.

Disclosures: K. Zubkow: None. **T.M. Poitras:** None. **A. Chandrasekhar:** None. **D.W. Zochodne:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.02/AA22

Topic: C.09. Brain Injury and Trauma

Support: CIHR

Title: Cellular dynamics in adult dorsal root ganglia

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Abstract: The identity, fate and role of the wider repertoire of perineuronal cells in dorsal root ganglia (DRG), other than satellite glial cells (SGCs), are largely unexplored. Here we examine dynamic cycling in DRGs of adult rats with or without remote axotomy injuries. We employed a well known marker of DNA turnover, ki67 and incorporation of Brdu to characterize cycling populations, emphasizing 3 day axotomized DRGs in SD rats. Brdu was given intraperitoneally immediately, then two days later following sciatic nerve transection. Cellular characterization was done using immunohistochemistry. As expected both ki67 and Brdu marked a subpopulation of $GFAP^+$ cells indicating SGC turnover, and that this turnover is enhanced after axotomy. Strikingly, they also marked selected cells of the $Iba1^+$ or $ED1^+$ macrophage population, indicating unappreciated local turnover of these populations. A striking observation was the

presence of the stem cell/dedifferentiation marker sox2 in perineuronal satellite cells. Sox2 was highly expressed in a majority of SGCs, irrespective of the cell cycle status, but was also colocalized to a smaller group of $Iba1^+$ or $ED1^+$ cells. A small proportion of sox2 expressing cells also co-expressed Brdu or ki67 indicating that they are actively cycling. We noted intimate contact between SGCs and macrophages in axotomized DRGs after 3 days of sciatic nerve transection. A time course analysis, post transection, showed that SGC activation precedes macrophage contact, rendering it unlikely that there is an initiating role for macrophages on SGC activation. However, *in vitro* co-culture of axotomy primed neurons, SGCs and macrophages identified macrophages wrapping around areas of neuronal debris indicating phagocytosis. Overall, the injured DRG perineuronal milieu favors multi-lineage cellular turnover, some of which involves sox2 and, involving SGCs and macrophages. Additionally, macrophages may play an important role in scavenging byproducts from rapid turnover of cells in the DRGs post axotomy. [Supported by CIHR]

Disclosures: A. Krishnan: None. **D.W. Zochodne:** None.

Poster

676. Peripheral Nerve Injury and Repair

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Program#/Poster#: 676.03/AA23

Topic: C.09. Brain Injury and Trauma

Support: Craig H. Nielsen Foundation

Title: Conditioning with botulinum toxin enhances motor axon regrowth in mouse and human models of injury

Authors: *C. K. FRANZ[1], L. JORDAN[1], J. A. ORTEGA[2], E. KISKINIS[3], C. HECKMAN[4]
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Abstract: Peripheral axon regeneration is improved when the nerve lesion under consideration has recently been preceded by another nerve injury. This is known as the conditioning lesion effect (CLE). While the CLE is one of the most well robust and well characterized means to enhance motor axon regeneration in experimental models, it is not considered a clinically feasible strategy. It is likely that the mechanism of the CLE is related to acute denervation changes. Therefore, we decided to test whether chemo-denervation with an FDA approved formulation of botulinum toxin A (BoTX-A) would be sufficient to reproduce the CLE with the goal of eventual clinical application. We examined the effects of a 1-week pre-conditioning administration of BoTX-A on motor axon regrowth in both a mouse tibial nerve injury and human stem cell-based model. We assessed axon regeneration in vivo (mice) with retrograde

tracers and histological analysis of peripheral nerve tissue after injections into the triceps surae muscle group. We assessed motor neurite outgrowth in vitro (human) by dissociation and re-plating stem cell-derived motor neurons for morphometric analysis. We found that BoTX-A conditioning treatment significantly enhanced outgrowth of motor axons/neurites in both our mouse and human models, which supports further preclinical development of this novel approach to enhance motor axon regeneration.

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Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.04/AA24

Topic: C.09. Brain Injury and Trauma

Support: CIHR

Title: Activation of TRPV1 receptors improves the regenerative capacity of adult sensory neurons

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Abstract: The influx of calcium generated by activation of TRPV1 neuron channels is generally linked to toxic axonal degeneration. However, subtoxic rises in axonal calcium, such as that generated by extracellular electrical stimulation paradigms, may be supportive of axon growth, and intracellular calcium gradients are known to influence growth cone behaviour. Here we asked whether subtoxic TRPV1 activation influenced the growth properties of adult sensory neurons and sensory axon regeneration after injury. TRPV1 activation through high dose (1 mM) capsaicin exposure of dissociated adult sensory neurons from rats rendered expected neuronal death and axon retraction. However, lower doses (10-100 µM) enhanced neurite outgrowth. Using calcium imaging, we confirmed that this degree of activation was associated with heightened calcium flux within neurons. We next tested whether or not a similar relationship between TRV1 activation and regeneration exists *in vivo.* We used a high sciatic crush mouse model, immediately followed by a single application of either a low (200uM) or high (2mM) dose of capsaicin directly to the site injury. At 28 days following injury and capsaicin, the low dose group showed a more rapid recovery of thermal but not mechanical sensation compared to vehicle treated controls. There were no significant improvements in animals treated with higher doses but instead we observed a further decline in sensory nerve conduction velocity. There was

no impact on sensory conduction velocity after low dose exposure and injury and neither dose improved motor function. Taken together, TRPV1 activation by sub-toxic doses of capsaicin causes increases in neuronal calcium influx, enhanced regeneration of injured sensory neurons, and improved behavioural recovery similar to that observed with paradigms of extracellular electrical stimulation.

Disclosures: T.M. Poitras: None. **A. Chandrasekhar:** None. **L. McCoy:** None. **C.A. Webber:** None. **D.W. Zochodne:** None.

Poster

676. Peripheral Nerve Injury and Repair

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Topic: C.09. Brain Injury and Trauma

Support: CIHR

University Hospital Foundation

Title: Electrical stimulation as a conditioning lesion for promoting peripheral nerve regeneration

Authors: *K. CHAN[1], J. L. SENGER[2], J. L. OLSON[2], C. A. WEBBER[3]
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Abstract: The beneficial effects of a preinjury crush conditioning lesion (CL) on peripheral nerve regeneration have been well-documented in animal models. Despite, that, no human studies have been attempted to date. Principle reasons are the ethical dilemma of deliberately injuring an intact nerve and the difficulty in predicting the timing of a nerve injury. Recent studies demonstrated that 1 hour of electrical stimulation (ES) produces effects similar to CL in neuronal cultures. This, coupled with the increasing use of nerve transfers, in which an intact nerve is deliberately cut to reinnervate a denervated muscle, means that ES may be clinically translatable to enhance regeneration. This study hypothesizes that ES prior to nerve injury will enhance nerve regeneration. Twenty-Four Sprague-Dawley rats were divided into four groups of 6 based on conditioning-type to the common peroneal (CP) nerve: ES, crush, sham-ES, and naïve. One week following conditioning, they underwent a cut/coaptation of the CP nerve at the sciatic trifurcation. On post-cut day 14, nerves and dorsal root ganglia (DRGs) were collected. Axonal counts of nerves stained with NF-200 revealed similar lengths of regeneration between ES and crush (4.2±0.6 mm vs. 4.3±0.4 mm, $p=0.66$) that were superior to sham-stimulation (1.2±0.4 mm) and naïve (1.1±0.3 mm, $p<0.05$). A greater number of axons at the distal tip were present in animals that received either ES or crush conditioning compared to the unconditioned

cohorts. To evaluate mechanisms, DRGs were stained with neuronal injury marker growth associated factor-43 (GAP-43), and satellite glial cells with glial fibrillary acidic protein (GFAP). Significant increase in GAP-43 expression at three days was observed in ES and crush cohorts compared to sham or naïve ($p<0.001$). The satellite glial cells of ES and crush conditioning showed a significant increase in GFAP expression (29.3% and 39.3% respectively) compared to sham (8.6%) and naïve (13.5%) DRGs. By demonstrating similar improvements in axon regeneration, this proof of principle study suggests that ES conditioning may produce regenerative outcomes comparable to the crush injury model. This would open the possibility of testing ES for conditioning lesion like effects in clinical trials prior to nerve surgery to enhance nerve regeneration.

Disclosures: K. Chan: None. **J.L. Senger:** None. **J.L. Olson:** None. **C.A. Webber:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.06/AA26

Topic: C.09. Brain Injury and Trauma

Title: A novel local FK506 delivery system enhances axon regeneration

Authors: *K. TAJDARAN[1], K. CHAN[2], M. S. SHOICHET[3], T. GORDON[4], G. H. BORSCHEL[5]
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Abstract: Purpose: Administration of FK506, an FDA approved immunosuppressant, has shown to enhance nerve regeneration following peripheral nerve injuries. However, the severe side effects of the systemically delivered FK506 has prevented clinicians from using this drug routinely. Therefore, we have developed a novel fibrin gel based local delivery system for FK506. In this study, we analyzed the effectiveness of the FK506 local delivery system to promote axon regeneration. In addition, we analyzed FK506 transport to the surrounding tissues, *in vivo*, from the delivery system at the nerve injury site. **Methods:** FK506 was incorporated into fibrin gel in solubilized, particulated or poly(lactic-*co*-glycolic) acid microspheres-encapsulated forms. A rat nerve transection model was used, where the proximal tibial nerve stump was cross-sutured to the distal stump of a cut common peroneal nerve. Rats in the negative control groups either did not receive any delivery system treatment or received fibrin gel with empty microspheres. The experimental groups included rats treated with fibrin gel loaded with the three forms of FK506 formulation. Three weeks after repair, nerve regeneration was assessed using

retrograde labeling and histomorphometric analysis. Using mass spectrometry, FK506 tissue concentrations were analyzed at the site of the nerve injury, in sciatic nerve, dorsal root ganglia (DRGs), spinal cord, brain, heart, liver, kidney, and plasma at 7, 14, and 28 days post repair. **Results**: Rats in experimental groups receiving FK506-loaded microspheres and the particulated FK506 had significantly highest number of motor and sensory neurons that regenerated their axons and allowing *all* tibial motoneurons regeneration. Histomorphometric analysis indicated increased number of myelinated axons following particulated FK506 and FK506 microspheres treatment compared to the negative control groups. The most prolonged period of FK506 *in vivo* release at the site of nerve injury was seen with the PLGA microsphere-encapsulated form for 28-days. The highest FK506 tissue concentration was detected within the entire spinal cord at day 7 regardless of the delivery system formulation. FK506 was also found at the nerve injury site, sciatic nerve, DRGs, and the gluteal muscles, decreasing in concentration over time, with little to no drug detection in other vital organs. **Conclusion**: The local application of FK506 via our proposed delivery systems resulted in excellent axon regeneration while minimizing the toxicity of systemic FK506 that has prevented clinicians from using FK506 routinely for treating severe cases of peripheral nerve injuries.

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Poster

676. Peripheral Nerve Injury and Repair

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Topic: C.09. Brain Injury and Trauma

Support: EU-FP7 project INMiND, grant number 278850

Title: MRI tracking of Gadoteridol-labeled mesenchymal stem cells in a spinal cord injury murine model

Authors: *M. M. BOIDO[1], M. FILIPPI[2], C. PASQUINO[3], F. GARELLO[2], C. BOFFA[2], E. TERRENO[2]
[1]Univ. of Turin, Orbassano (TO), Italy; [2]Mol. and Preclinical Imaging Ctr., Torino, Italy; [3]Mol. Biotech. Ctr., Torino, Italy

Abstract: Mesenchymal Stem Cells (MSCs) are multipotent stromal cells, able to deliver neurotrophic, anti-inflammatory and immunomodulatory molecules: for these reasons, their effects are exploited for the treatment of a multitude of pathologies, including neurodegenerative diseases and traumatic CNS lesions. In case of spinal cord injury (SCI), the regrowth of severed axons is limited, but cell therapy can promote circuit repair, reorganization and axonal sprouting.

Imaging-supported in vivo cell tracking provides a reliable method to assess the characteristics of cell grafts and to monitor the cell growth/movement after transplantation. In this study, murine MSCs were labeled with the clinically approved MRI agent Gadoteridol through a procedure based on the hypo-osmotic shock (hypo-MSCs), in order to be tracked in vivo in a murine model of SCI. Moreover in vitro and in vivo analysis have been performed to evaluate cell viability, proliferation and surface marker expression of MSCs. With respect to iso-osmotic incubations, the hypo-osmotic labeling did not alter the biological and functional profile of MSCs in vitro, but significantly increased the Gadoteridol cellular uptake. In vivo imaging on SCI mice revealed a substantial T1 contrast enhancement after transplantation of 300,000 labeled MSCs, enabling to circumscribe their spinal distribution and to follow their migratory dynamics for about 10 days. Histological validation of in vivo data corroborated the imaging results, highlighting the opportunity to perform a precise and reliable monitoring of the cell-based therapy. Finally, animals treated with labeled MSCs were monitored by behavioral tests and showed motor improvements, confirming the unaltered therapeutic efficacy of hypo-MSCs. Our results suggest that the presented cell labeling procedure is endowed with high efficacy and clinical translatability, and could possibly be beneficial for stem cell-based medical protocols required in tissue repair.

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Poster

676. Peripheral Nerve Injury and Repair

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: NSF Graduate Fellowship

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Title: Modeling epidural spinal cord stimulation to predict paraplegic patients' responses and identify critical features of the electrical activity

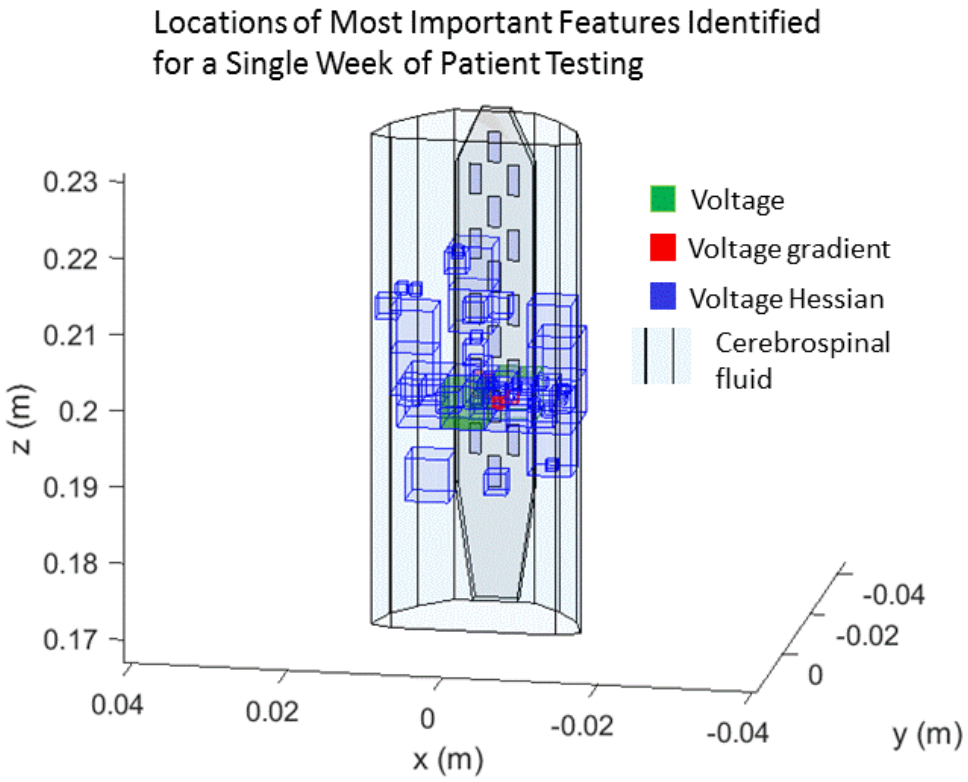
Authors: *E. R. FELDMAN, Y. SUI, J. W. BURDICK
Computing and Mathematical Sci., Caltech, Pasadena, CA

Abstract: Spinal cord stimulation (SCS) applied by multi-electrode epidural arrays implanted over the lumbosacral spinal cord has enabled paraplegics to stand and regain partial motor control. This work links computational SCS models to experimental data obtained by testing

paraplegic subjects' standing performance under various stimuli. Machine learning techniques applied to the dataset and simulation results isolate stimulation characteristics associated with good empirical motor recovery via SCS. These results may help to clarify some of the mechanisms underlying the success of SCS and to suggest new methods to guide the selection of effective stimuli for each patient.

The standing skill of two paraplegic subjects implanted with 16-electrode epidural implants was tested in response to 90 and 117 different stimuli respectively over two non-consecutive weeks. Using a volume conductor model of the spinal cord, we calculated by finite element analysis the electric field and current densities that should occur within the spinal tissues under each experimentally-tested stimulus. We constructed a set of features from the average values of the voltage amplitude, gradient, and Hessian in tissue voxel grids of several granularities. Via random forest and elastic net regression, we show that these features can predict the subjects' empirical responses. We also applied feature selection methodology to identify the features most correlated with, and that most likely influenced, the subject responses.

We find that the key electric field features are anatomically structured (see figure) and agree with neural activation theory. Further analysis, using a novel feature selection approach, highlights groups of spinal tissue locations that may be co-activated during effective posture control. Finally, we show that Gaussian process regression can effectively model a probability distribution on the performance of candidate stimuli, allowing more informative performance prediction for untested stimuli. This result could help clinicians identify stimuli with a high probability of success.



Disclosures: **E.R. Feldman:** None. **Y. Sui:** None. **J.W. Burdick:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.09/AA29

Topic: C.09. Brain Injury and Trauma

Support: NIH R01 NS09697

NSF CBET - 1402984

Title: Cortex-dependent recovery of unassisted hindlimb locomotion after complete spinal cord injury in adult rats

Authors: *K. A. MOXON[1,2], G. FOFFANI[3], P. D. GANZER[4], V. BRACCHI-RICARD[2], J. R. BETHEA[2], A. MANOHAR[2]
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Abstract: After paralysing spinal cord injury the adult nervous system has little ability to "heal" spinal connections, and it is assumed to be unable to develop extra-spinal recovery strategies to bypass the lesion. We challenge this assumption, showing that completely spinalized adult rats can recover unassisted hindlimb weight support and locomotion without explicit spinal transmission of motor commands through the lesion. This recovery is achieved with combinations of pharmacological and physical therapies that maximize cortical reorganization, inducing an expansion of trunk motor cortex and forepaw sensory cortex into the deafferented hindlimb cortex. This cortical reorganization is characterized by altered levels of proteins associated with synaptic plasticity supported by astrocyte function, and sprouting of corticospinal axons. Lesioning the reorganized cortex reverses the recovery. Adult rats can thus develop a novel cortical sensorimotor circuit that bypasses the lesion, likely through biomechanical coupling, to partly recover unassisted hindlimb locomotion after complete spinal cord injury. These results demonstrate the importance of plasticity along the entire neural axis to optimize recovery of function.

Disclosures: K.A. Moxon: None. **G. Foffani:** None. **P.D. Ganzer:** None. **V. Bracchi-Ricard:** None. **J.R. Bethea:** None. **A. Manohar:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.10/AA30

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH Grant NS30226

Title: Stretch-induced activation of muscles paralyzed by spinal cord injury

Authors: *C. K. THOMAS, L. MONTOYA, K. GANT
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Abstract: Many people with spinal cord injury (SCI) report that repeated, sustained passive stretch is an effective way to manage muscle spasms because the stretch triggers spasms then reduces them. Physical therapists often use this stretch approach to manage contractures. Our aim was to examine how paralyzed muscles (under no voluntary control) respond to repeated, sustained passive stretch by recording surface electromyographic (EMG) signals (vastus lateralis, hamstrings, tibialis anterior, medial gastrocnemius, soleus) and joint angles (knee, ankle) during experimenter-induced passive stretch of the four muscle groups (10 static stretches, each held for 30 seconds, release, 15 seconds rest between stretches). The recordings were repeated on a different day but without stretch. Data were compared to results obtained from uninjured (control) subjects. Most muscles responded to the changes in muscle length (lengthening or shortening). The EMG responses were usually stronger in SCI participants, particularly during the rest phase, suggesting a lack of inhibition. The EMG responses occurred with each stretch, without habituation, and spread to arm and hand muscles in SCI individuals. Thus, repeated stretch of muscles is an effective way to exercise paralyzed muscles. Contraction intensity was not related to the maximal soleus H-reflex to M-wave ratio, suggesting that small diameter afferents, not necessarily Ia afferents, underlie the muscle responses to stretch.

Disclosures: C.K. Thomas: None. **L. Montoya:** None. **K. Gant:** None.

Poster

676. Peripheral Nerve Injury and Repair

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Program#/Poster#: 676.11/AA31

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS076589

NIH Grant R01NS090622

VA Grant I01RX000815

VA Grant I01RX001807

Craig H. Neilsen Foundation Grant 261299

Title: Robotic upper-limb assessment of bilateral asymmetries after spinal cord injury

Authors: *A. WILSON[1,2], Y. LEI[1,2], M. A. PEREZ[1,2]
[1]Dept. of Neurolog. Surgery, The Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL; [2]Bruce W. Carter Dept. of Veterans Affairs Med. Ctr., Miami, FL

Abstract: Cervical spinal cord injury (SCI) in humans largely damages both sides of the spinal cord resulting in asymmetrical impairments in arm function (Oxland et al., 2010; Calabro and Perez, 2016). The purpose of our study was to use the Kinesiological Instrument for Normal and Altered Reaching Movement (KINARM) exoskeleton device to assess asymmetries in upper-limb function in individuals with chronic incomplete cervical SCI. Maximum isometric voluntary contraction (MVC) was quantified in upper-limb muscles including the first dorsal interosseous, abductor pollicis brevis, extensor and flexor digitorum communis, biceps and triceps brachii and anterior and posterior deltoid to determine the stronger and weaker arm in SCI participants. Using the KINARM arm position matching task we quantified the systematic shift between the passive and active hands, the spatial contraction/expansion area of the active hand relative to the passive hand, and trial-to-trial variability of the active hands end position between trials. While all variables were affected in SCI participants compared with control subjects, we found that the systematic shift was the variable that better reflected asymmetries in MVC between the arms of SCI subjects (controls: right arm= 4.3±2.1 cm, left arm=2.8±1.2 cm; SCI: weaker arm=7.1±2.1 cm, stronger arm=6.5±2.3 cm). Our findings suggest that the KINARM can effectively detect functional asymmetries in upper-limb function in humans with chronic SCI. This new assessment tool may increase the sensitivity of current upper-limb clinical assessment following SCI.

Disclosures: **A. Wilson:** None. **Y. Lei:** None. **M.A. Perez:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS076589

NIH Grant R01NS090622

VA Grant I01RX000815

VA Grant I01RX001807

Craig H. Neilsen Foundation Grant 261299

Title: Contribution of the corticospinal pathway to spasticity following spinal cord injury

Authors: *R. A. MACKLIN[1,2], R. A. OZDEMIR[1,2], M. A. PEREZ[1,2]
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Abstract: Spasticity is one of the most common symptoms in humans with spinal cord injury (SCI). The neurophysiological and behavioral outcomes related to its clinical assessment, however, remain poorly understood. Here, we examined the Modified Ashworth Scale (MAS; a gold standard clinical assessment of spasticity), Wartenberg's Pendulum Test, and the H-reflex (H-max) and maximal motor response (M-max) in the quadriceps muscle in individuals with SCI who had residual voluntary activity (incomplete SCI, n=18) and in those unable to voluntarily activate muscles below the level of injury (complete SCI, n=18). We found that the MAS was higher in individuals with incomplete (2.34±1.15, $p<0.001$) compared with complete (0.76±0.74) SCI. The H-max and M-max were larger in individuals with incomplete compared with complete SCI and control subjects. The knee joint angular velocity was less pronounced in individuals with incomplete compared with complete SCI, suggesting that individuals with incomplete SCI had more pronounced spasticity. To further understand the physiological mechanisms contributing to spasticity in individuals with complete SCI who showed spasticity (MAS=3) and no spasticity (MAS=0) we examined the integrity of the corticospinal pathway by using transcranial magnetic and electrical stimulation over the leg motor cortex and measuring motor evoked potentials (MEPs) in the quadriceps muscle. Notably, we found that MEPs elicited by magnetic and electrical stimulation were present in individuals with complete SCI who had severe spasticity but absent in individuals with complete SCI without spasticity. Altogether our results suggest that transmission in the corticospinal pathway contributes to spasticity in humans with chronic incomplete SCI.

Disclosures: R.A. Macklin: None. **R.A. Ozdemir:** None. **M.A. Perez:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.13/AA33

Topic: C.09. Brain Injury and Trauma

Support: Grant-in-Aid for Scientific Research

Title: GLP-1 receptor agonist enhances the ER stress response and improves functional recovery after spinal cord injury in a rat model

Authors: *S. NOMURA[1], H. KATOH[2], S. YANAGISAWA[2], T. IMAI[3], M. KUROIWA[4], M. WATANABE[2]
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Abstract: After spinal cord injury (SCI), oligodendrocyte precursor cells (OPC) residing in the spinal cord have been shown to actively proliferate, but many these cells succumb to apoptosis instead of differentiating into functional oligodendrocytes. One of the factors involved in neural cell apoptosis is endoplasmic reticulum (ER) stress, which arises from the accumulation of misfolded proteins in the ER. We previously reported that enhancing the ER stress response by administering amiloride improved OPC survival and differentiation, enhanced remyelination, and improved hind limb motor and sensory dysfunction.
Glucagon-like peptide-1 (GLP-1) receptor agonists, which are used in the treatment of type 2 diabetes, have recently been shown to exhibit neuroprotective effects and to decrease ER stress. The aim of this study is to examine the effect of the GLP-1 receptor agonist exenatide on the ER stress response in the injured spinal cord and on functional recovery.
A moderate contusive SCI was induced in 10-week-old female Sprague-Dawley rats using an IH-impactor (200 Kdyne). The GLP-1 group received subcutaneous injections of 10 μg exenatide immediately after and 7 days after SCI, while the control group received no treatment. Blood glucose levels were monitored and hind limb motor function was evaluated using the BBB score. At 1, 3, 7, and 14 days after SCI, spinal cords were excised (n=5 per group) and the expression of GRP78, which acts to decrease ER stress, and CHOP, which induces apoptosis in response to severe ER stress, were examined using Western blot.
Blood glucose levels rose sharply immediately after SCI and then gradually descended to approximately 100 mg/dl by 12 hours after SCI. No significant difference was observed between the two groups, and hypoglycemia was not observed in the GLP-1 group. Western blot revealed a significant increase in GRP78 expression on Day 3 ($p<0.01$), and a significant decrease in CHOP expression on Day 14 ($p<0.05$) in the GFP1 group compared to the control group. BBB scores revealed significantly higher motor scores in the GLP-1 group from day 7 and later ($p<0.01$).
Our results show that administration of the GLP-1 receptor agonist exenatide decreased ER stress and led to significant improvement of hind limb motor function. Since GLP-1 receptor agonists are in clinical use with other documented characteristics that would potentially be beneficial to the recovery after SCI, we believe that GLP-1 receptor agonists are a very promising candidate for the pharmacological treatment of SCI.

Disclosures: **S. Nomura:** None. **H. Katoh:** None. **S. Yanagisawa:** None. **T. Imai:** None. **M. Kuroiwa:** None. **M. Watanabe:** None.

Poster

676. Peripheral Nerve Injury and Repair

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Program#/Poster#: 676.14/AA34

Topic: C.09. Brain Injury and Trauma

Support: Taylor Foundation for Chronic Diseases

VA Career Development Award (1-IK2-RX-001123-01-A2)

PVA Research Foundation

Title: Gene therapy to alleviate hyperreflexia after spinal cord injury

Authors: C. A. BENSON, M. HILL, S. LIU, F. DIB-HAJJ, S. G. WAXMAN, S. DIB-HAJJ, *A. M. TAN
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Abstract: Spasticity is a symptom of *hyperexcitability* within the spinal stretch reflex system (e.g., H-reflex), and is a frequently observed secondary impairment following spinal cord injury (SCI) and other insults to the CNS. Spasticity generally presents as a velocity-dependent increase in muscle tone and uncontrolled, repetitive, involuntary contractions of skeletal muscles. Despite its prevalence and negative impact on quality-of-life, spasticity is only incompletely understood and represents and unmet medical need. Conventional anti-spasticity drugs, such as baclofen, can provide relief of spastic symptoms, but have significant limitations. In contrast, the availability of viral-mediated gene manipulation in the nervous system offers three distinct advantages: 1) increased target tissue specificity, 2) reduced off-target effects, and 3) prolonged therapeutic efficacy.
Over the past decade, we have gathered a large body of evidence demonstrating a strong correlation between abnormal dendritic spine morphology and hyperexcitability disorders associated with SCI, i.e., neuropathic pain and spasticity. Dendritic spine changes associated with pain or a loss of H-reflex rate-dependent depression (RDD) indicative of spasticity, include 1) an increase in spine density, 2) a redistribution of spines to regions closer to the cell body, and 3) an increase in dendritic spine head surface area. Collectively, our findings support the premise that dendritic spine dysgenesis serves as a morphological correlate to understand and address spasticity following SCI. We have recently identified the Rac1-Pak1 molecular pathway as a potential candidate for pharmacological intervention.
Here we will present our data in developing a novel gene therapy to elucidate the abnormal

cellular mechanisms that underlie H-reflex circuit hyperexcitability. Our data show that intramuscular delivery of an adeno-associated virus (AAV) targeting Rac1 expression infects motor neurons of the spinal cord and permits fluorescent image analysis of dendritic spine dysgenesis. Using EMG recordings, we show that viral-mediated treatment appears to reduce hyperexcitability in the stretch reflex system. This preclinical study is in-progress with an overall objective of deconstructing the mechanisms underlying spasticity at the circuit-level within the injured spinal cord.

Disclosures: C.A. Benson: None. **M. Hill:** None. **S. Liu:** None. **F. Dib-Hajj:** None. **S.G. Waxman:** None. **S. Dib-Hajj:** None. **A.M. Tan:** A. Employment/Salary (full or part-time):; Yale University, Department of Veterans Affairs.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.15/AA35

Topic: E.09. Spinal Cord Injury and Plasticity

Support: FAPESP 2014/06892-3

FAPESP 2015/26206-0

CNPq 300552/2013-9

Title: Recovery of sensory-motor integration after dorsal rhizotomy and repair with platelet-rich plasma (PRP)

Authors: *M. V. DE CASTRO, B. B. VOLPE, Â. C. M. LUZO, A. L. R. OLIVEIRA
Univ. of Campinas (UNICAMP), Campinas, Brazil

Abstract: Motor coordination involves specific neural processes ranging from the perception of stimuli to the achievement of the response, being dependent on delicate sensory-motor integration, which is particularly evident in the spinal cord. Spinal root injuries can lead to motor, sensibility and autonomic losses. This type of lesion constitutes a significant medical problem and usually affects the brachial plexus in consequence of high energy trauma. However, due to the possibility of generating further inflammation and neuropathic pain, surgical procedures do not prioritize the repair of the afferent component. In this context, new therapies need to be developed for dorsal root repair. A promising treatment would be the use of platelet-rich plasma (PRP). Nowadays, PRP is used in a wide range of surgical procedures, and there are several scientific studies demonstrating benefits in treating various types of injuries. Therefore, to investigate the effectiveness of PRP as adhesive and inductive element for nerve regeneration, adult female Lewis rats (LEW/HsdUnib; n=5 per group) were subjected to unilateral rhizotomy

(RZ) of the L4–L6 dorsal roots and divided into two groups: (1) RZ without repair; (2) RZ followed by root repair with PRP (RZ+PRP). The reflex arc recovery was evaluated daily through the electronic von-Frey method, during eight weeks, while the expression of VGLUT1 (vesicular glutamate transporter 1), GFAP (astrocyte marker) and Iba-1 (microglial marker), was evaluated in the spinal cord by immunofluorescence, eight weeks after lesion. Taken together, our results indicate that PRP is efficient to repair transected spinal roots, restoring the reflex of paw withdrawal, without signs of allodynia (8th-week post-lesion*: RZ+PRP= 65.13% better than RZ*). Also, the use of PRP for this type of injury allowed the reentrance of primary afferents within the spinal cord and did not exacerbate the glial reactivity, promoting the restoration of spinal circuits. We believe that our results will serve as a basis for the use of PRP in accelerating nerve regeneration and may contribute to the future clinical use of this therapeutic approach, fulfilling a critical gap in reparative procedures after this type of injury.

Disclosures: M.V. De Castro: None. **B.B. Volpe:** None. **Â.C.M. Luzo:** None. **A.L.R. Oliveira:** None.

Poster

676. Peripheral Nerve Injury and Repair

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Topic: C.09. Brain Injury and Trauma

Support: Taylor Foundation for Chronic Diseases

VA Career Development Award (1-1K2-RX-001123-01-A2)

PVA Research Foundation

Title: Therapeutic targeting of Pak1 signaling alleviates neuropathic pain after traumatic 2nd degree burn injury

Authors: Y.-Q. GUO[1], *P. EFFRAIM[2,3], C. BENSON[1], S. HENRY[1], S. G. WAXMAN[4], S. D. DIB-HAJJ[5], A. M. TAN[6]
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Abstract: Across the globe, 11 million individuals per year require medical treatment due to severe burn injuries. However, chronic intractable pain that arises following cutaneous burn trauma is rarely studied in preclinical models. To investigate mechanisms related to burn-injury neuropathic pain, we developed a highly-reproducible model in mice, which produces persistent

pain. In this model, histological assessment of the burned glabrous skin of the hind paw confirmed that the procedure results in a 2nd degree burn-injury that fully penetrates the epidermis and portions of the dermis. Within three days after burn injury, mice exhibit significant mechanical allodynia and heat hyperalgesia that persists for up to 4 weeks. Dendritic spine dysgenesis, a morphological correlate of nociceptive hyperexcitability and neuropathic pain, appeared within the intermediate zone of the dorsal horn. In addition, we observed an increase in the ipsilateral expression of c-fos, GFAP (astrogliosis), and Iba1 (microgliosis). Our previous work has implicated a role for the Rac1 molecular signaling pathway in dendritic spine dysgenesis underlying neuropathic pain in several models of neuropathic pain, including SCI, peripheral nerve injury, and diabetic neuropathy. Rac1 belongs to the Ras superfamily, a class of GTPases which are generally considered poor clinical targets due to their complex intracellular dynamics. To accelerate translation of our preclinical findings, we sought to establish a proof-of-principle that targeting Pak1, a downstream effector of Rac1, can disrupt abnormal dendritic spine remodeling and alleviate neuropathic pain symptoms. FK228 (romidepsin) at 0.1-1nM concentrations significantly reduces PAK1 kinase activity. Our interim data in our model of burn injury demonstrate that systemic administration of romidepsin can downregulate expression of p-raf1, a Pak1 effector target, reduce the degree of dendritic spine dysgenesis, and partially rescue thermal or mechanical pain thresholds. Finally, we observed a significant decrease in burn-injury induced c-fos and GFAP expression ipsilateral to the side of the burn following romidepsin treatment. Taken together, our findings merit further investigations of Pak1 signaling as a potential molecular target for therapeutic intervention in traumatic burn-injury induced neuropathic pain.

Disclosures: Y. Guo: None. **P. Effraim:** None. **C. Benson:** None. **S. Henry:** None. **S.G. Waxman:** None. **S.D. Dib-Hajj:** None. **A.M. Tan:** None.

Poster

676. Peripheral Nerve Injury and Repair

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Topic: C.09. Brain Injury and Trauma

Support: FPR-Hampshire College CBD Program

Hampshire College Denice O'Neill Scholarship Fund

Title: Effects of injury-induced histamine release on fibroblasts and the extracellular matrix in peripheral nerves

Authors: *J. RAUCH, M. ANEX-SCHNAUSS, C. GILL, J. CASTORINO
Hampshire Col., Amherst, MA

Abstract: Histamine secreted by mast cells promotes fibrosis by increasing type I collagen production and inducing fibroblast proliferation and migration. Peripheral nerve fibroblasts share many of the same characteristics as fibroblasts in these tissues; therefore, histamine may affect peripheral nerve fibroblasts in a similar way. The aim of this experiment was to study the effect of histamine on collagen, fibronectin, laminin, and transforming growth factor-β; mRNA expression in 3T3 fibroblasts and to determine a role for histamine in peripheral nerve regeneration following injury. NIH-3T3 fibroblasts were starved in medium containing 1% DBS and DMEM for 36 hours, prior to induction for 12 hours with 2% DBS and DMEM ± 10^{-4} M histamine. Total RNA extractions and qRT-PCR were performed to determine mRNA expression. Our results show that histamine-treatment increased Col1a1 (p = 0.158), Fn1 (p = 0.222), and Lamb1 (p = 0.048) mRNA expression and decreased Tgfb1 (p = 0.360) mRNA expression in 3T3 fibroblasts. No significant difference in fibroblast number was observed between control and histamine-treated cultures. Furthermore, adult rat sciatic nerves were cultured over a confluent layer of 3T3 fibroblasts and completely transected with or without histamine. After 5 days of live tissue imaging, nerves were fixed, stained with collagen type I alpha 1 chain and laminin subunit beta 1 primary antibodies, and imaged by fluorescence microscopy. We show nerve outgrowth over the course of 5 days and demonstrate differences in ECM matrix deposition between histamine-treated and control nerves. The observed significant upregulation of LAMβ;1 mRNA expression in response to histamine is a novel finding. Contrary to previous research, our data indicates that histamine has no significant effect on cell number and type I collagen production. Furthermore, our results provide additional evidence that the histamine released by mast cell activation plays a critical role during peripheral nerve injury.

Disclosures: J. Rauch: None. **M. Anex-Schnauss:** None. **C. Gill:** None. **J. Castorino:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.18/BB2

Topic: E.09. Spinal Cord Injury and Plasticity

Title: Bidirectional paired-associative synaptic plasticity at spinal motoneurons

Authors: *A. YAMASHITA
Neurorehabilitation Res. Institute, Morinomiya, Osaka-Shi, Japan

Abstract: Introduction: Paired-associative stimulation (PAS), repeated transcranial magnetic stimulation (TMS) pairing with electrical peripheral nerve stimulation (ES), leads to synaptic plasticity at the cortical level. The direction and magnitudes of induced plasticity are dependent on interstimulus intervals. Here we investigated synaptic plasticity at spinal motoneurons (SMs) using a modified PAS protocol, named as SM-PAS.

Methods: Eleven right-handed healthy volunteers participated in this study. Motor-evoked potentials (MEPs) were recorded from right first dorsal interosseous muscle (FDI). Peripheral ES was delivered on right ulnar nerve at the wrist, and stimulus intensity was set at supramaximal intensity. TMS was applied over the left primary motor cortex (M1) hand area, and stimulus intensity was set at 120% resting motor threshold for the right FDI. We measured TMS-evoked MEP and F-wave latencies in each subject and calculated difference in latencies to determine an appropriate timing which overlaps TMS-induced descending volleys with ES-induced antidromic inputs at the SM synapses. We performed SM-PAS (180 pairs at 0.2 Hz) at different intervals of TMS and ES pairing. For evaluating corticospinal-motoneuronal synaptic excitability, single-pulse TMS was delivered at cervicomedullary junction level during brief contraction of the right FDI, and cervicomedullary MEP (CMEP) was recorded from the right FDI before and after SM-PAS every 10min for 1 hour. Cortical MEP by TMS of the left M1 hand area, compound muscle action potential (CMAP) and F-waves by ulnar nerve stimulation were also measured from right FDI.
Results: When the interval was set at the timing at which antidromic inputs in the motoneurons axons reached the neurons just before the corticospinal descending volley arrived at the presynaptic terminal, SM-PAS facilitated CMEPs for 60 min. Inversely, SM-PAS reduced CMEPs for 60 min when antidromic inputs reached the postsynaptic terminal 9 ms after the descending volleys arrival. MEP tend to increase after facilitatory SM-PAS, but this effect was not statistically significant. F/M ratio remained unchanged after SM-PAS.
Discussion: Here we successfully induced the synaptic plasticity at the corticospinal-motoneuronal synapses by applying SM-PAS. The direction and magnitudes of induced plasticity are in line with spike-timing dependent plasticity rule. Lack of significant increase of cortical MEP after SM-PAS may reflect homeostatic compensatory changes in cortical excitability to cancel out the altered spinal excitability.

Disclosures: **A. Yamashita:** A. Employment/Salary (full or part-time):; Neurorehabilitation Research Institute, Morinomiya Hospital,.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

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Program#/Poster#: 676.19/BB3

Topic: C.09. Brain Injury and Trauma

Support: JSPS 15H05041

JSPS 23390461

Title: Semaphorin3A inhibits axon regeneration after trigeminal nerve transection

Authors: *H. KANEMARU[1], K. SEO[2], Y. YAMADA[3], A. OHAZAMA[4], T. MAEDA[5]
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Abstract: [Introduction]
Semaphorin 3A (Sema 3A) is one of secreted proteins involved in axonal guidance during embryo as well as in regeneration of spinal cord injury after birth and detrimental. Although the expression of Sema 3A has been found in human neuroma after spinal nerve injury (Tannemaat 2007), functional significance of Sema 3A remains unclear in detail during the peripheral nerve regeneration.
[Aims]
The present study examined a chronological change in expression of Sema 3A in the injured lesion after inferior alveolar nerve (IAN) transection to reveal its roles in the process of peripheral nerve regeneration.
[Material and methods]
This study used a nerve injury model using male C57BL6 mice (7~8 weeks) as we have previously reported. Briefly, under deep anesthesia by 4% chloral hydrate, after the masseter muscle was tone to expose the surface of the mandible, its bone was removed by a dental drill to expose the IAN. Then, IAN was cut at distal site of mandibular formation.
(1) Expression of Sema 3A; mice were allowed to survived for 1, 3, 7, 14 days after the operation, and they were perfused with fixative. Cryostat sections of the IAN were processed for Sema 3A immunohistochemistry (antibody ab23393) with by TSA amplify Kit.
(2) Immunohistochemical observation of effects by Sema 3A antagonist; either antibody to Sema 3A or vehicle (physiological saline) was locally administered to the legion at postoperative day (PO) 1 and 2. Animals were perfused with fixative at PO3. Cryostat sections were immunostained with an antibody to PGP9.5, a general marker for nerve fibers, to examine the regeneration lesion.
(3) Retrograde tracer study on effect of Sema 3A antagonist; Either Fluoro-Gold or DiI was injected to the mental area prior to IAN cut and at PO5, respectively. At PO7, the expression of the tracers was observed in the trigeminal ganglion.
[Results]
(1) Sema 3A expression was detectable only at the medial site of the IAN lesion. This expression could be found at PO1, but it decreased at PO3. No expression appeared after PO7.
(2) The vehicle control animals demonstrated widely-randomized axon sprouting from the medial bulb of the transected IAN at PO3. However, Sema 3A antagonist suppressed such axon sprouting.
The animals administrated with Sema 3A antagonist appeared to exhibit more FG expression in the trigeminal ganglion, suggesting an acceleration of axon regeneration.
[Conclusion]
Immunoexpression of Sema 3A was recognizable at the medial site of the damaged nerve immediately after the injury, and thereafter diminished. It is implicated that Sem 3A contributes

to inhibit axon regeneration only at the early stage of nerve regeneration.
Supported by JSPS 15H05041 & 23390461

Disclosures: H. Kanemaru: None. **K. Seo:** None. **Y. Yamada:** None. **A. Ohazama:** None. **T. Maeda:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.20/BB4

Topic: C.09. Brain Injury and Trauma

Title: Axon regeneration promoted by signaling of the unfolded protein response in peripheral nerve injury

Authors: *Y. OHTAKE[1,2], A. SAITO[2], K. IMAIZUMI[1]
[1]Dept. of Biochem., [2]Dept. of Stress Protein Processing, Hiroshima Univ., Hiroshima-Shi, Japan

Abstract: The endoplasmic reticulum (ER) has a dynamic interconnected network responsible for maintaining cellular homeostasis including local calcium ion concentration, lipid metabolism and protein synthesis. Multiple cellular malfunctions such as disturbance of calcium ion homeostasis and expression of mutated proteins perturb ER functions. The abnormalities are known as ER stress. The three major ER stress transducers IRE1, PERK and ATF6 recognize ER stress, followed by transducing signals to activate protein quality control system and avoid cellular damages. This signaling pathway is referred to as unfolded protein response (UPR). The UPR is involved not only in ER homeostasis but also in regulating biological functions. Recent studies indicate that the UPR is activated in response to axonal injury, suggesting the prospective association of the UPR derived from the developed axonal ER network with axon regeneration and degeneration. In this study, we investigated the mechanisms for inducing ER stress in response to axon injury and the roles of UPR in regulating axon regeneration in sensory neurons. To assess the effect of the UPR signaling on axon regrowth, we used axotomized neurons of mouse dorsal root ganglion (DRG) at embryonic day 13 and a mouse model of sciatic nerve crush. The phosphorylation levels of IRE1 and PERK were up-regulated in primary cultured DRG after axonal injury. The inhibition of calcium ion release from ER by 2-APB and dantrolene reduced the phosphorylation of those transducers. These data suggest that at least one of the underlying factors for the activation of UPR after the injury is calcium ion release from ER and its depletion in axonal ER lumen. We observed the activation of IRE1 and PERK in distal sites of axons in response to sciatic nerve crush. The attenuation of those was exhibited by the pre-treatment of axons with 2-APB and dantrolene after sciatic nerve crush, consistent with those in primary cultured DRG neurons. Axonal regrowth of primary cultured DRG neurons and sciatic nerve was reduced by the pre-treatment of axons with specific inhibitors of ER stress

transducers. We found that the blocking of UPR signaling by the inhibitors of ER stress transducers promoted the ER fragmentation in distal axons. Consequently, axonal injury-induced UPR signaling at an axonal segment has a potential to promote axon regeneration through the proper manipulation of axonal ER dynamics, that could maintain the ER functions and the integral ER-derived signaling pathways for eliciting the regeneration.

Disclosures: Y. Ohtake: None. **A. Saito:** None. **K. Imaizumi:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.21/BB5

Topic: C.09. Brain Injury and Trauma

Support: Adelson Medical Research Foundation

Title: GMFb may regulate the Schwann cell repair phenotype after acute and chronic denervation

Authors: *J. SCHEIB[1], A. HOKE[2]
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Abstract: The peripheral nervous system (PNS) has the capability of regenerating over long distances. However, full functional recovery is often limited, especially when the target tissue is far away. After injury, Schwann cells take on a repair cell phenotype, resulting in debris clearance, growth factor secretion, and maintenance of basal lamina tubes to guide axons. In nerve injuries where axons must regenerate long distances, the chronically denervated distal Schwann cells become atrophied and less supportive of regeneration, but the molecular mechanisms of this atrophy are unknown. In this study, we hypothesize that glia maturation factor beta (GMFb), a pro-inflammatory mediator mostly studied in astrocytes, is involved in the repair cell phenotype of Scwhwann cells. Our preliminary data suggest that GMFb expression is increased in rat sciatic nerves after injury, but this upregulation is not maintained after chronic denervation. GMFb overexpression in cultured rat Schwann cells protects them from apoptosis, and may alter debris clearance. We are further analyzing the phenotypic changes of cultured Schwann cells with overexpression of GMFb, and we are using mouse models to study the effects of altered GMFb expression on nerve regeneration in vivo.

Disclosures: J. Scheib: None. **A. Hoke:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.22/BB6

Topic: C.09. Brain Injury and Trauma

Support: March of Dimes Foundation's Gene Discovery and Translational Research Grant

Title: 3D printing aligned scaffold immobilizing bioactive cue for neural regeneration

Authors: *W. ZHU[1], F. MASOOD[3], B. T. HARRIS[4], L. ZHANG[2]
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Abstract: Nerves are ease of getting damaged through disease, trauma, and congenital defects. The self-regenerative capacity of nervous system is extremely limited. Therefore, artificial intervention is usually needed to address most severe nerve injuries. Although the use of autograft (a nerve harvested from a less important site of a patient), presents partially regenerative outcomes, it often leads to complication including donor site morbidity. Tissue engineered scaffolds which involve biomaterials, cells and bioactive cues are showing promise to repair damaged neural tissues with functional recovery. In this present study, we utilized a stereolithography based 3D printing technique to generate novel tissue engineered scaffolds containing highly aligned micro channels for neural regeneration. The printable bioink is composed of natural plant oil based biomaterial which is sustainable and biocompatible. In addition, bioactive cues, such as bFGF (basic fibroblast growth factor) and EGF (epidermal growth factor), were immobilized on the printed scaffolds by polydopamine (PD) in an effort to promote neural cell adhesion, and direct neuronal differentiation. The 3D printed scaffolds we fabricated with varied channel densities and infills demonstrated well-defined highly aligned microstructure. Confocal microscopy images indicate the plant oil based bioink presents exceptional biocompatibility and the high channel densities on the scaffolds aid mesenchymal stem cell growth with aligned orientation. PD coating is able to enhance surface adsorption of protein, improve scaffold hydrophilicity, and promote cell proliferation after 5 day culture. Additionally, neural differentiation of mesenchymal stem cells was observed on bioactive cues immobilized scaffolds. In conclusion, stereolithography based 3D printing technique is able to print aligned scaffolds by using plant oil based biomaterial. By immobilizing bioactive cues, the resultant scaffolds present the capacity in directing cell alignment, promoting cell proliferation and inducing neural differentiation of stem cells, providing great potential for neural tissue engineering applications.

Disclosures: W. Zhu: None. **F. Masood:** None. **B.T. Harris:** None. **L. Zhang:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.23/BB7

Topic: C.09. Brain Injury and Trauma

Support: K08NS067282

Title: Temporal relationships of behavioral, electrophysiological and pathological outcomes with *In vivo* muscle physiology during motor unit reconnectivity

Authors: *C. G. WIER[1,2], A. R. KNAPP[2], P. L. HEILMAN[2], W. ARNOLD[3], S. J. KOLB[4,2]
[1]Chris Wier, Columbus, OH; [2]Dept. of Biol. Chem. and Pharmacol., Ohio State Univ., Columbus, OH; [3]Neurol., The Ohio State Univ., Columbus, OH; [4]Neurol., The Ohio State Univ. Wexner Med. Ctr., Columbus, OH

Abstract: Background: Peripheral nerve injury (PNI) results in weakness by disrupting the connection of motor axons with muscle fibers. Complete functional recovery of the motor axonal connectivity is rarely achieved in patients with more severe PNI. One critical gap in our current knowledge is the molecular determinants of motor neuron repair. To address this gap, there is a need to have a reliable, comprehensive and longitudinal understanding of motor unit physiology that is paired with behavioral and pathological outcomes. Standard electrophysiological measures such as compound muscle action potential (CMAP) or motor unit number estimation (MUNE) allow tracking of recovery and commonly used in both clinical and preclinical studies. Here we aimed to understand the relationship in recovery between electrophysiological and muscle physiological outcomes.
Objective: To determine the longitudinal relationships between standard peripheral nerve recovery outcome measures and *in vivo* muscle physiology.
Design: Sciatic nerve was performed in adult FVB mice. Behavioral motor assessment (sciatic function index), electrophysiological assessment of motor unit connectivity (CMAP and MUNE), and muscle physiological status (tetanic plantar flexion torque) were monitored longitudinally during recovery. Outcome measures were followed up to 28 days post-injury (28dpi). Pathological characterization of neuromuscular junction (NMJ) reinnervation was performed at 21dpi. Statistical comparison was performed from functional nadir at 7dpi. Correlation between measures was assessed using Pearson correlation coefficient.
Results: At 18 dpi, significant improvement was noted in both CMAP amplitude and the SFI ($p<0.01$). In contrast, MUNE and plantar flexion torque did not show significant improvement until 21dpi ($p<0.05$ and $p<0.01$, respectively). There was good correlation between the plantar flexion torque measurements and both CMAP ($r=0.60$, $p<0.01$) and MUNE ($r=0.62$, $p<0.01$). Quantification of NMJ reinnervation is ongoing.

Conclusion: In our studies, CMAP and behavioral outcomes were able to identify the earliest signs of recovery. In contrast, our findings suggest that assessment of muscle physiology and motor unit electrophysiology may be more effective at identifying persistent neurological deficits in mouse models of nerve injury and repair.

Disclosures: C.G. Wier: None. **A.R. Knapp:** None. **P.L. Heilman:** None. **W. Arnold:** None. **S.J. Kolb:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

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Program#/Poster#: 676.24/BB8

Topic: C.09. Brain Injury and Trauma

Support: NSF Grant EEC-0812348

NSF Grant NCAT 260116C

American Academy of Otolaryngology, the American Association of Hand Surgeons (AAHS) Annual Research Grant

Title: Peripheral nerve repair with magnesium metal filaments providing contact guidance support

Authors: X. AN[1], T. M. HOPKINS[2], J. J. VENNEMEYER[2], A. M. HEILMAN[2], K. J. LITTLE[4], D. B. HOM[3], *S. K. R. PIXLEY[2]
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Abstract: To repair peripheral nerves after injuries that cause gaps, optimized biomaterial scaffolds are sought to replace the current gold standard, autografts. To perfect scaffolds, we hypothesized that biodegradable metallic magnesium (Mg) filaments (<1mm diameter), placed inside nerve conduits, would provide contact guidance support for regenerating cells and axons. *Methods:* To determine if this was possible, experimental gaps made in one sciatic nerve of adult Lewis rats were repaired by placing nerve stumps in hollow poly(caprolactone) (PCL, immersion dipped) or silicone conduits. Groups received either a single Mg filament (99.9% Mg, d=250μm) touching both nerve stumps inside a saline filled conduit, a similar titanium (Ti) filament (same d), no filaments (empty, negative controls) or isografts (positive controls). Imaging via microCT was done at 6 weeks to assess Mg degradation, in either tissues or living animals. Animals were sacrificed at 6 weeks for 10 mm gaps and after 14-16 weeks for gaps of 15 mm (supposedly a critical gap length with conduits alone). For all animals, behavioral testing included foot sensory

and motor function tests and measurements of the widest calf circumference to monitor muscle atrophy. At sacrifice, calf muscles were weighed and nerves and conduits were either osmicated or treated with iodine for soft tissue imaging by microCT. Tissues (some after iodine removal) were paraffin or resin embedded and processed for histological and antibody staining. *Results:* Significant gaps were seen in almost all Mg filaments by 6 weeks, with few conditions showing slower degradation, i.e., intact filaments. In all cases, regenerating tissues clearly encapsulated and surrounded Mg filaments, with no signs of necrosis and very low stimulation of macrophages. Improved axon amounts and size (determined by neurofilament 200 protein immunostaining) occurred with Mg filaments and a 10 mm gap, compared to Ti filaments or empty conduits. With longer gaps of 15 mm and after 14-16 weeks, Mg filaments were completely resorbed. Functional improvement and muscle atrophy reversal occurred only with isograft groups, not with Mg or empty conduits. Nerve tissue spanned the gaps in most animals (including empties). No scarring or increased fibrosis was found after Mg degradation was complete. General tissue health was significantly enhanced with Mg over empty conduits, with less inflamed blood vessels. Overall, biodegradable Mg filaments are biocompatible and show promise for providing contact guidance and improving tissue regeneration in peripheral nerve repair.

Disclosures: X. An: None. **T.M. Hopkins:** None. **J.J. Vennemeyer:** None. **A.M. Heilman:** None. **K.J. Little:** None. **D.B. Hom:** None. **S.K.R. Pixley:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.25/DP04/BB9 (Dynamic Poster)

Topic: C.09. Brain Injury and Trauma

Title: Two-photon imaging of human neuromuscular junction degradation after traumatic peripheral nerve injury

Authors: *J. P. CHAN, W. A. PALISPIS, O. STEWARD, R. GUPTA
Univ. of California, Irvine, Irvine, CA

Abstract: Introduction: The study of the neuromuscular junction as a model for synaptogenesis as well as other disease states is fundamental in neuroscience. Remarkably there is NO information about the time course and nature of human neuromuscular degeneration. Patients with traumatic peripheral nerve injuries provide a unique opportunity to capture this invaluable data as we sought to provide the novel data about human motor endplate degeneration at the neuromuscular junction (NMJ).
Methods: IRB approval was obtained so as to permit biopsies from denervated muscles in patients with injuries ranging from complete pre-ganglionic C5-T1 brachial plexus injuries to

less severe, but distinct, traumatic nerve injuries. Specimens were processed for immunohistochemistry and visualized with two-photon excitation and confocal microscopy. Human muscle samples from multiple timepoints after injury were analyzed along with control specimens from innervated muscles so as to create a temporal sequence of events for human motor endplate degradation following traumatic nerve injury.
Results: Denervated muscle samples show distinct differences from innervated muscles, including fragmentation and dispersion of acetylcholine receptors. There is also a noted decrease in NMJ volume as seen in 3D reconstruction, and a trend towards plaque endplate morphology. Moreover, comparison of denervated muscles shows signs of temporal degeneration. NMJs from early denervated muscles still show well preserved circular morphology with definite acetylcholine receptors arranged in distinct folding patterns. By one year status post traumatic brachial injury, NMJs begin to present with greater fragmentation. Moreover, synaptic gutters start to fade, and asymmetry in acetylcholine receptor distribution is noted. Interestingly, even after one year of denervation, NMJs were able to retain their overall circular shape.
Conclusion: This study details the novel and critically important qualitative data about the sequence of events involved in human motor endplate degradation after a clearly defined traumatic nerve injury. Surprisingly, human NMJs persist and retain their structures even after the 6-month window of opportunity for meaningful functional recovery has elapsed, which may indicate a limited utility of animal models for traumatic peripheral nerve injuries. This temporal profile highlights the importance of species-specific findings and provides invaluable data that can answer important questions pertaining to the optimal timing of surgical intervention and timing of any adjuvant treatments for peripheral nerve injuries.

Disclosures: **J.P. Chan:** None. **W.A. Palispis:** None. **O. Steward:** None. **R. Gupta:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.26/BB10

Topic: C.09. Brain Injury and Trauma

Support: NIH Grant

Title: Tissue engineered nerve grafts maintain distal pro-regenerative Schwann cells in a rodent model of chronic axotomy

Authors: *D. BROWN[1,2], Z. ALI[2], J. BURRELL[2], K. KATIYAR[2], K. BROWNE[2], D. CULLEN[2]
[1]Neurosurg., [2]Ctr. for Brain Injury and Repair, Dept of Neurosurg., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Peripheral nerve injury (PNI) is a common affliction that affects individuals of all age groups and socioeconomic backgrounds. However, current repair strategies yield limited functional restoration, especially when axon s are tasked with regenerating over long distances that require many months to reach targets. A primary reason for insufficient regeneration involves the breakdown of distal Schwann cells (SCs), the resident glial cells that provide trophic and structural support for regenerating axons. After axotomy and subsequent Wallerian degeneration, distal SCs become temporarily pro-regenerative, but absent regenerating axons and associated molecular cues the chronically denervated SCs lose their pro-regenerative capabilities over several months. To address this need, we are exploring the potential of “satellite” transplants containing living neurons and axonal tracts as a means to integrate with otherwise axotomized SCs and thereby maintain their pro-regenerative capacity. To test this concept, the sciatic nerve was transected and the proximal nerve stump was capped to block regenerating host axons from reaching the distal stump. Custom three-dimensional neuronal/axonal constructs were placed within nerve guidance tubes (NGTs) and implanted in-line with the distal stump either at the time of transection or following a delay of 6 or 10 weeks (negative control animals received a NGT without cells). All animals were euthanized at 16 weeks after the initial transection and the distal nerves were processed for immunohistochemical examination of SC presence and morphology. We found that implants exhibited robust neuronal survival and axonal growth throughout the otherwise axotomized sciatic, tibial, common peroneal, and sural nerves in animals with acute or delayed implants. The presence of TENG axons correlated with increased levels of pro-regenerative SCs in each of the nerves relative to NGT controls, as indicated by SC alignment and immunoreactivity for p75 and S100. The area of pro-regenerative SCs was quantified in fascicles of each nerve, revealing that the effects of neuronal/axonal implants versus NGTs in preserving SCs was most pronounced in the tibial, common peroneal, and sural branches over 3 cm distal to the transection site, indicating that these constructs successfully “babysat” SCs far afield from the implantation site. We are currently coupling this distal SC “babysitting” strategy with additional tissue engineered constructs designed to bridge segmental defects to ascertain the ability of this dual approach to accelerate axonal regeneration and enable functional recovery following currently intractable PNI.

Disclosures: D. Brown: None. **Z. Ali:** None. **J. Burrell:** None. **K. Katiyar:** None. **K. Browne:** None. **D. Cullen:** None.

Poster

676. Peripheral Nerve Injury and Repair

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 676.27/BB11

Topic: C.09. Brain Injury and Trauma

Title: N6-Methyladenosine (m6A) translationally regulates the regenerative capacity

Authors: *Y.-L. WENG[1], R. AN[1], T. XU[2], J. CASSIN[1], X. WANG[1], C. VISSER[1], F. ZHANG[2], P. JIN[3], H. WU[2], X. ZHUANG[4], C. HE[5], H. SONG[6], G.-L. MING[7]
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Abstract: mRNA translation is an essential process for successful axon regeneration. This machinery controls local protein synthesis at the injury site and generates newly synthesized proteins in the cell body to promote axon ourgrowth. Although the spatiotemporal protein abundance is determined by a sophisticated coordination of transcriptional levels and translation efficiency, the underlying mechanisms that direct translational regulation of intrinsic growth ability remain unclear. In this study, we examined whether N6-Methyladenosine (m6A), an RNA modification involved in regulating mRNA translation and stability, was involved in axon regeneration. We performed m6A-Seq of naïve and axotomized dorsal root ganglions (DRGs) and found that RNA methylation occurred on a repertoire of regeneration-associated genes (RAGs). Mettl14 is one of the methylases that catalyze the methylation of mRNA. In Mettl14KO mice, the m6A containing transcripts are reduced. Moreover, we revealed an impairment of axon outgrowth upon injury in the DRGs of Mettl14 KO mice. Taken together, our results suggest that m6A may play an important role in the of the regulation of growth capacity and uncover new potential targets for promoting axon regeneration.

Disclosures: Y. Weng: None. **R. An:** None. **T. Xu:** None. **J. Cassin:** None. **X. Wang:** None. **C. Visser:** None. **F. Zhang:** None. **P. Jin:** None. **H. Wu:** None. **X. Zhuang:** None. **C. He:** None. **H. Song:** None. **G. Ming:** None.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 677.01/BB12

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIA T32 AG000222

BrightFocus Foundation

NIH AG026249

Title: Tau induces formation and dysfunction of small diameter capillaries in aged tau P301L mice

Authors: *R. E. BENNETT, A. B. ROBBINS, B. T. HYMAN
Neurol., Massachusetts Gen. Hosp. Dept. of Neurol., Charlestown, MA

Abstract: Alzheimer's disease pathology is characterized by amyloid beta plaques, tau-containing neurofibrillary tangles and neuronal cell death. Mounting evidence indicates that these changes are exacerbated by vascular abnormalities with cerebral amyloid angiopathy, hypertension, cholesterolemia, and diabetes being among the best known contributors to weakened and dysfunctional cerebral vasculature (BUÉE et al., 1997; Kalaria, 1999; Zipser et al., 2007). The contribution of tau neurofibrillary tangle pathology to vascular change is less clear. To examine this relationship between tau and blood vessels, we performed in vivo two-photon imaging to assess blood vessel changes in tau-overexpressing mice carrying the P301L tau mutation (rTg4510). Aged transgenic mice exhibited a significant increase in blood vessel density at 15-18 months and a reduction in average blood vessel diameter from 5.8 ± 1.5 microns in controls to 3.9 ± 0.1 microns in Tg4510 mice. These small diameter vessels were also blocked by rhodamine 6G-labeled leukocytes in 25% ± 4% of capillaries in Tg4510 mice compared to 7% ± 3.5% in control mice. Blocked vessels contained plasma only and were not observed to have red blood cell flow. We hypothesized that these small diameter, apparently non-functional vessels were either collapsed "string vessels" or were newly formed capillary tubes. To test this, we then isolated CD31+ endothelial cells from the brain and performed qPCR analysis which indicated gene expression changes related to angiogenesis including increased *VegfA, Serpine1*, *Plau*, and *Mmp9*. Similar changes were confirmed in human gene expression data sets comparing patients with high tau tangle pathology versus low tangle pathology. Altogether, this indicates a novel pathway whereby pathological changes due to tau accumulation induce aberrant angiogenesis in the brains of Alzheimer's disease mouse models and human patients. Further, blockage of small diameter blood vessels by leukocytes could explain, in part, observed cerebral hypoperfusion in Alzheimer's disease.

Disclosures: R.E. Bennett: None. **A.B. Robbins:** None. **B.T. Hyman:** None.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 677.02/BB13

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Brightfocus A2015296S

NIH F31 1F31AG050409-01A1

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Department of Defense grant W81XWH-13-MRPRA-CSRA

UL1TR001108 from the National Institutes of Health, National Center for Advancing Translational Sciences.

Title: TREM2 deficiency results in early exacerbation of tau pathology and leads to enhanced neurodegeneration with cognitive deficits in hTau mice

Authors: *S. M. BEMILLER[1], T. J. MCCRAY[1], K. ALLAN[2], A. L. OBLAK[1], G. XU[1], O. N. KOKIKO-COCHRAN[3], S. D. CRISH[4], R. M. RANSOHOFF[5], G. E. LANDRETH[1], B. T. LAMB[1]

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Abstract: Recent identification of the R47H coding variant of the Triggering Receptor Expressed on Myeloid Cells-2 and its conferral of increased risk of developing late onset Alzheimer's Disease (LOAD) has led to a surge of research investigating the role of TREM2 in regulating CNS pathologies. TREM2 is a critical immune regulating protein normally expressed exclusively in the CNS on microglia and infiltrating peripheral myeloid populations which enter the diseased CNS. Recent work by the Lamb lab has identified a role for TREM2 in regulating amyloid pathology in transgenic APPPS1 and 5XFAD mice by using novel *Trem2*$^{LacZ/+}$ and *Trem2*$^{lacZ/LacZ}$ mice (*Trem2*$^{-/-}$). We demonstrated that TREM2 deficiency leads to time dependent alterations in plaque load, decreasing hippocampal plaque load at 4-months of age, and ultimately exacerbates widespread regional plaque pathology later in disease. Additionally, TREM2 deficiency results in chronic altered inflammatory gene expression profiles and decreased microglial survival late in pathology. Despite the advances in understanding the role of TREM2 in regulating amyloid pathologies, very little is known regarding the role of TREM2 in regulating the other cardinal hallmark of Alzheimer's Disease pathology, namely the intraneuronal inclusion of hyperphosphorylated and aggregated microtubule associated protein tau (Tau). In order to explore the hypothesis that TREM2 signaling plays protective roles in modifying tauopathy, we crossed the *Trem2*$^{-/-}$ mice to humanized tau mice which express all six isoforms of human tau and are lacking endogenous murine tau (hTau mice). Here we demonstrate that TREM2 deficiency results in exacerbated and hastened tau phosphorylation and aggregation by 6-months of age along with dysregulated kinase activity. This phenomenon persists throughout pathology and results in modest cognitive dysfunction by 12-months of age, and ultimately dramatic neurodegeneration by 18-months. Further, these phenomena are directly related to inefficient microglial mediated inflammatory responses due to TREM2 deficiency. Our results suggest a critical role for TREM2 in regulating the pathological outcomes in tauopathy and represent an exciting potential novel therapeutic target.

Disclosures: **S.M. Bemiller:** None. **T.J. McCray:** None. **K. Allan:** None. **A.L. Oblak:** None. **G. Xu:** None. **O.N. Kokiko-Cochran:** None. **S.D. Crish:** None. **R.M. Ransohoff:** None. **G.E. Landreth:** None. **B.T. Lamb:** None.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 677.03/BB14

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Grant-in-Aid for Science Research on Innovation Area ("Brain Protein Aging" 26117001) from the Ministry of Education, Culture, Sports, Science and Technology, Japan

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Strategic Research Program for Brain Sciences from Japan Agency for Medical Research and development, AMED, Japan

Title: Investigating combinatory phosphorylation of tau in propagation models of tauopathy

Authors: *N. SAHARA[1], T. KIMURA[1], G. MATSUMOTO[2]
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Abstract: Filamentous tau aggregates are the histopathological hallmark of tauopathy. Recently, the hypothesis of tau protein propagation in tauopathy is widely accepted. However, it is still unclear whether tau phosphorylation can be propagated in a clonal fashion. The purpose of this study is to verify if there is a combinatory tau phosphorylation pattern during the transduction of tau inclusions in both cells and mice. We developed stable cell lines expressing both full-length four repeat tau isoform and K18-GFP (GFP tagged 4 repeat domain of tau) with P301L FTDP-17 mutation. To introduce intracellular inclusions, heparin induced tau aggregates consisting of P301L mutated K18 were transduced into stable cell lines. After subcloning, stable cell lines with intracellular inclusions were established. Phosphorylation and insolubility of tau protein in each cell line was examined by Phos-tag SDS-PAGE and sedimentation assay, respectively. As a result, we found different phosphorylation pattern with distinct intracellular inclusions. Once a specific phosphorylation pattern of propagating tau protein is defined, findings will provide useful information to control prion-like transmission and spreading of tau pathology. Further examinations are ongoing to validate the propagation of tau phosphorylation in vitro and in vivo.

Disclosures: **N. Sahara:** None. **T. Kimura:** None. **G. Matsumoto:** None.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 677.04/BB15

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Alzheimer's Association Research Grant

Title: GPRC6A linked mTORC1 activation impacts tauopathies

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Abstract: Tauopathies are a group of neurodegenerative diseases characterized by pathognomonic protein inclusions formed by abnormal accumulation of microtubule-associated protein named tau. Tau inclusions are observed as intracellular neurofibrillary tangles. Clinical phenotypes of tauopathies manifest as cognitive impairment and behavioral disturbance. The aggregation of tau remains a central target for drug discovery, however no disease-modifying treatments exist. The mechanistic target of rapamycin (mTOR) signaling has emerging evidence in regulating all aspects of cellular proteostasis in response to diverse stresses through the uncovered cytosolic and lysosomal L-arginine sensing pathways, respectively. Our group has discovered a unique interaction between tau aggregation and mTOR signaling linked to L-arginine metabolism. In both human Alzheimer’s disease patient samples and tau transgenic mice, we observed dysregulated L-arginine metabolism and uncoupled mTOR signaling proteins associated with tau pathology. The depletion of L-arginine by overexpressing arginase 1 significantly reduced tau pathology in transgenic mice. We speculate that hyperactivity of mTOR signaling impairs proteostasis and exacerbates neuropathology. G protein coupled receptor (GPCR) family C, group 6 member A (GPRC6A) was recently deorphanized by basic L-amino acids, especially L-arginine. Although the exact role of GPRC6A remains unknown, we posit that GPRC6A mediates extracellular sensing of L-arginine to regulate mTOR complex 1 (mTORC1) signaling. We hypothesize that decreased GPRC6A signaling inhibits mTORC1 activation, thus clearing tau during tauopathies. We posit that GPRC6A remains tonically active and senses extracellular L-arginine in tauopathies. By utilizing tau overexpressing cell lines and tau transgenic mice, we blocked GPRC6A activity with novel allosteric antagonists and downregulated GPRC6A expression via shRNA constructs. We found that both pharmacological allosteric antagonism and genetic downregulation of GPRC6A inhibited mTORC1 signaling, promoted proteostasis and significantly reduced total monomeric and oligomeric tau in tauopathy

cells. Overall, our data suggests that decreased GPRC6A signaling reduces tau pathology. This is the first study to uncover the mTORC1 signaling mediated by extracellular sensing of L-arginine through GPRC6A. Further studies are required to warrant the exact mechanism of GPRC6A in maintaining proteostasis in tau transgenic mice. Therapeutics that modulate GPRC6A activity may potentially provide new treatments to clear protein aggregates in tauopathies and other proteinopathies.

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Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

Location: Halls A-C

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Program#/Poster#: 677.05/BB16

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant : 5R01NS042023-13

Title: Hexosamine pathway metabolites ameliorate tauopathy in *C. elegans* neurons

Authors: *E. PARK, I. TARIQ, C. RONGO
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Abstract: The microtubule-associated protein Tau is implicated in Alzheimer's Disease (AD) and various tauopathies, often forming hyperphosphorylated aggregates and fibrillary tangles, yet the mechanism by which Tau impairs neuron function remains controversial. One well-characterized tauopathy is frontotemporal dementia with parkinsonism-chromosome 17 (FTDP-17), patients with which have Tau mutations, including V337M (hTauV337M). In *C. elegans*, neuronal overexpression of hTauV337M combined with an aggregation-promoting fragment of Tau (F3ΔK280, which includes amino acids 258-360 but deleted for K280) results in Tau aggregation and uncoordinated locomotive behavior with multiple axonal defects[1]. Here we examine the effect of expressing hTauV337M and F3ΔK280 on microtubule-based transport in the command interneurons. Animals that express mutant Tau have fewer mitochondria, as well as defective transport of presynaptic synaptobrevin-1 (SNB-1) and postsynaptic AMPA receptors (GLR-1) to glutamatergic synapses. Interestingly, introduction of a Kinesin-Tom7 chimeric protein, which directly couples mitochondria to the microtubule track without the need of motor adaptors, improves mitochondria distribution in motor neurons, suggesting that mutant Tau acts by impairing the ability of mitochondria to associate with kinesin motors. To examine the role of Tau aggregation in this process, we exposed animals to conditions that reverse protein aggregation, including manipulation of the hexosamine pathway. The hexosamine pathway can

be activated by increasing the synthesis of N-acetyl glucosamine, resulting in enhanced proteostasis and the reduced effects of age-related diseases [2]. We found that the genetic activation of the hexosamine pathway or supplementation with the pathway metabolite N-acetylglucosamine reduces Tau aggregation, improves locomotion, and increases neuronal mitochondrial number compared to the untreated group. Our study suggests that promoting proteostasis by enhancing the hexosamine pathway could be potential therapeutic strategy to treat Tauopathy.

1. Fatouros, C. *et al.* Inhibition of tau aggregation in a novel Caenorhabditis elegans model of tauopathy mitigates proteotoxicity. *Hum Mol Genet* **21**, 3587-3603, doi:10.1093/hmg/dds190 (2012).
2. Denzel, M. S. *et al.* Hexosamine pathway metabolites enhance protein quality control and prolong life. *Cell* **156**, 1167-1178, doi:10.1016/j.cell.2014.01.061 (2014).

Disclosures: E. Park: None. **I. Tariq:** None. **C. Rongo:** None.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

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NIGMS T32 Training Grant in Biomolecular Pharmacology

Title: Knockdown of RNA binding protein TIA1 rescues RNA dysregulation and protects against tau mediated neurodegeneration in the PS19 P301S tau mouse model of Alzheimer's disease

Authors: *B. MAZIUK[1], D. APICCO[1], A. CRUZ-LOURDES[1], E. VAN VLIET[1], N. YAZDANI[1], L. GOLDBERG[1], M. MEDALLA[1], C. LEBLANG[1], C. ZHANG[2], C. UNG[2], N. M. KANAAN[3], H. LI[2], C. BRYANT[1], J. LUEBKE[1], T. IKEZU[1], B. WOLOZIN[1]

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Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disease characterized by severe deficits in memory, thinking and behavior. At the molecular level, AD is characterized by two hallmark pathologies: the development of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs). In particular, NFTs are formed from tau, a microtubule binding protein expressed in neurons throughout the brain. During AD pathogenesis, hyperphosphorylated tau aggregates into oligomers and eventually pathological fibrils. However, the molecular mechanisms which drive the development of tau pathology remain elusive. Recently, the Wolozin lab has identified ribonucleoprotein granules, particularly stress granules (SGs), as major components of AD pathology which coincide with the development of tau pathology. For instance, T-cell intracellular antigen 1 (TIA1) is a primary SG nucleating protein which co-localizes with neuropathology in Amyotropic Lateral Sclerosis (ALS), AD, and frontotemporal dementia (FTD).

Following this discovery, we bred TIA1 heterozygous and homozygous knockouts of the PS19 P301S tau mouse model of tauopathy to determine if TIA1 reduction could ameliorate the development of tau pathology. We report that both heterozygous and homozygous deletion of TIA1 in PS19 mice improved memory performance, using the Y maze spontaneous alternation and novel object recognition tasks. Additionally, immunohistochemical (IHC) analysis indicated that loss of TIA1 also rescued the loss of synaptic markers such as synaptophysin. Further signs of rescue was observed with RNAseq. Analysis of transcription and splicing by RNAseq revealed a profound disturbance of RNA splicing in the PS19 model, which was rescued by deletion of TIA1 in the +/- and -/- mice. Analysis of tau pathology, though, showed a surprising result. The PS19 x TIA1+/- and -/- mice exhibited a striking increase in the number of NFTs in the brain, observed with antibodies to phospho-tau (PHF1, CP13) as well as with the pathological NFT markers, the Gallyas silver stain and Thioflavine, despite the behavioral rescue observed. Biochemical fractionation revealed a corresponding increase in insoluble tau with a notable decrease in tau oligomers. Studies of in vitro tau aggregation using electron microscopy demonstrated the ability of tau TIA1 to stabilize tau oligomers while inhibiting tau fibrillization. These results suggest that TIA1 preferentially binds and stabilizes oligomeric tau, while inhibiting the formation of fibrillar tau. This suggests a novel mechanism for regulating the pathophysiology of tau pathology that involves RNA and RNA binding proteins.

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Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

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Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Mext KAKENHI grant 15K09310

CREST from JST

Mext Scientific Research on Innovation Area, (Brain Protein Aging and Dementia control)

AMED SRPBS

AMED Brain/MINDS

Title: Aberrant interaction between FUS and SFPQ in 4R-tau dominant tauopathy brains

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Abstract: Fused in sarcoma (FUS) is genetically and clinicopathologically linked to frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). We have previously reported that FUS and SFPQ regulate alternative splicing of Mapt gene at exon10 which generates two pathogenic isoforms of neural microtubule-associated protein tau (Tau) protein. Silencing of FUS or SFPQ resulted in the increased ratio of 4-repeat tau (4R-tau)/ 3-repeat tau (3R-tau) followed by abnormal FTLD-like behavioral impairments, accumulation of phosphorylated tau, and neuronal loss. Therefore, we investigated the interaction between FUS and SFPQ in postmortem autopsied brains of FTLD and progressive supranuclear palsy (PSP) patients. The immunohistological analysis revealed that both FUS and SFPQ were localized in frontal neuron nuclei and hippocampal dentate gyrus (DG) neurons in all cases. Detailed quantification of the fluorescent signal intensities in the respective nuclei revealed that intra-nuclear co-localization of FUS and SFPQ was significantly reduced in FTLD and PSP compared to controls. The protein expression of FUS and SFPQ in postmortem brain tissue from FTLD, PSP, and control cases was also investigated. Immunoprecipitation analysis showed reduced interactions between FUS and SFPQ in the brains of FTLD and PSP patients. Our findings suggest that a pathophysiological link between FUS/SFPQ involved in the pathogenesis of FTLD and 4R-tauopathy.

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Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

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Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Ohio University Honors Tutorial College

Ohio University Research Committee

Provost Undergraduate Research Fund

Title: Utilizing fly primary neurons to study htau propagation: An *In vitro* model of alzheimer's disease

Authors: E. MURPHY, C. QIAN, C. QI, M. SMARELLI, R. YAVORSKY, A. LEE, D. LEE, *R. A. COLVIN
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Abstract: Aggregates of the microtubule stabilizing protein, tau, are found in the neurofibrillary tangles (NFTs) of Alzheimer's Disease (AD) patients. When phosphorylated, the protein is altered from an endogenous form to a pathogenic form. These aggregations, or tauopathies, are known to disrupt cell transport and destabilize the microtubule in its diseased state. Although these tauopathies have been accepted by the scientific community as a potential cause of AD, the mechanisms behind which this aggregated tau protein can spread and further the progression of the disease are unknown. New evidence suggests that these pathogenic forms of tau can infect neighboring neurons in a prion-like manner, meaning they have the potential to induce a conformational change in a normal tau protein, altering it to a diseased state. This trans-synaptic propagation is a hypothesized method of propagation in AD neurons. The purpose of this research project is to investigate the cellular mechanisms of propagation of tau in a cellular model of Alzheimer's Disease. Our preliminary results have shown that a *Drosophila* primary cell model can be used to express an aggregation prone pathogenic version of human tau protein (2N4R) in cholinergic neurons *in vitro*. This human tau isoform was integrated with a FLAG tag to allow for immunofluorescent visualization. Expression of hTau was confirmed by western blot of highly specific immunoprecipitated adult fly brain protein and in primary culture neurons by immunofluorescence using an anti hTau antibody. Tau protein was released extracellularly by inducing membrane depolarization in primary cultured neurons after incubation with KCl in the

media (conditioned media). Neurons were incubated with 50 mM KCl for four hours or 10 mM KCl for 24 hours. A fluorescence intensity assay measuring tau protein level after KCl treatment suggested that these neurons had a lower level of intracellular hTau when compared with untreated, 2N4R expressing neurons. Western blot analysis of the immunoprecipitated conditioned media (using hTau antibody) and then probed with AT180 demonstrated that released tau was phosphorylated. Addition of this conditioned media to control neurons (Cha-GFP) demonstrated cellular uptake of hTau protein into the soma. These results suggest that our model may be useful for studying the release and uptake of tau protein occurring in AD pathogenesis.

Disclosures: E. Murphy: None. **C. Qian:** None. **C. Qi:** None. **M. Smarelli:** None. **R. Yavorsky:** None. **A. Lee:** None. **D. Lee:** None. **R.A. Colvin:** None.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

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Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

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NSFS Grant 17ZR1408100

Title: miR-125b contributes to Tauopathy in Presenilin1/2 conditional knockout dementia model mice via NCAM

Authors: *B. MENG, L. ZHANG, H. DONG, B. MEI
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Abstract: Presenilin1 (PS1) and presenilin2 (PS2) are two members of γ-secretase, which notably processes Amyloid β precursor protein (APP), highly involved in familial Alzheimer's disease (FAD) pathology. Conditional forebrain PS1/PS2 double knockout (DKO) mice show cognitive capability impairments, affective disorder, severe forebrain shrinkage, inflammation, tau hyper-phosphorylation etc., but no Aβdeposition because of the complete dysfunction of γ-secretase, therefore was regarded as a unique Aβ-independent dementia mice model.
Among the dys-regulated microRNAs, miR-125b showed a significant up-regulation in prefrontal cortex (PFC) of DKO mice. We further confirmed that neural cell adhesion molecule (NCAM) was one of its targets by Dual Luciferase Reporter Assay. NCAM protein level was decreased when miR-125b was over-expressed (OE) in NGF-induced differentiated PC12 cells.

Moreover, with serum deprivation, up-regulation of pGSK3β-Ser9 resulted in a high activity of GSK3β in differentiated mir-125b-OE PC12 cells; which further led the hyper-phosphorylation of Tau, as well as the increased Caspase-3 activation, which were consisted with the situation in DKO mice. Finally, we introduced retroviral mediated miR-125b over-expression in the PFC of wildtype C57B/L6 mice which resulted learning deficiency in the Novel Objective Recognition task with a decreased density of dendritic spines. And similarly as in vitro, elevated activity of GSK3β and hyper- phosphorylation of tau protein were confirmed.
Taken together, with γ-secretase dysfunction, abnormally increased miR-125b inhibits the expression of NCAM that further caused the increase of downstream molecule GSK3β activity and tau hyper-phosphorylation further. Our results revealed mechanism of PS1/PS2 dysfunction effect on Tauopathy via microRNA regulation in an Aβ-independent manner in dementia.

Disclosures: B. Meng: None. **L. Zhang:** None. **H. Dong:** None. **B. Mei:** None.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

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Program#/Poster#: 677.10/BB21

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Microtubule affinity regulating kinase 2 inhibition: Synthetic peptide mimetic of human tau repeat domain reduces tau phosphorylation in rat primary cortical neurons

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Abstract: The microtubule-associated protein tau stabilizes microtubules by interacting with tubulins in neurons. Tau that is post-translationally phosphorylated can dissociate from tubulin, leaving polymeric microtubule structures in highly dynamic states. Tau phosphorylation at specific amino acids is precisely regulated by tau kinases and tau phosphatases. When this machinery is dysregulated, tau can be hyper-phosphorylated. Prolonged dissociation of hyper-phosphorylated tau induces microtubule collapse and disrupts axonal transport. More critically, diffusible tau can form prion-like oligomers, which have been implicated in the pathogenesis of age-dependent neurodegenerative diseases such as Alzheimer's disease (AD). Elevated activity of tau kinases, including microtubule affinity regulating kinase 2 (MARK2), has been demonstrated during AD pathogenesis. MARK2 is known to phosphorylate tau in one of four repeat (R) domains. Our objective was to develop synthetic peptide mimetics of human tau R1 domain (tR1) as non-cytotoxic, cell-permeable ligands to selectively inhibit MARK2-mediated phosphorylation of the endogenous tau. tR1 peptides showed minimal effects on viability when added to primary cortical neurons at concentrations up to 100μM. Antibody-based fluorescence polarization assays were used to demonstrate that our tR1 peptide mimetic was a ligand of

MARK2 *in vitro*. We observed that fluorescently labeled tR1 peptides were internalized by primary cortical neurons and localized in endosome-like vesicles throughout the soma and neurites, which can be inhibited by sodium azide, suggesting internalization by an endocytotic pathway. Phenylarsine oxide (PAO) treatment upregulated MARK2 activity and increased endogenous tau Ser262 phosphorylation significantly over untreated controls. Interestingly, co-treatment of PAO-treated cells with tR1 peptide and endosomal disruptors bafilomycin A1 or chloroquine reduced MARK2-dependent tau phosphorylation at Ser262 partially but significantly. Notably, tR1 peptide did not change phosphorylated tau level at Thr231. Taken together, these data suggest that tR1 peptides are internalized by cortical neurons and inhibit MARK2-dependent phosphorylation of endogenous tau at Ser262 when delivered to the cytosol. Importantly, these results show that the synthetic tR1 peptide mimetics are capable of selectively inhibiting tau phosphorylation at specific kinases-dependent sites. We anticipate that synthetic tR1 peptide will serve as strong leads in the development peptide-based AD therapeutics and as tools to study the complex nature of tau biology.

Disclosures: C. Qian: None. **N. Al Qaeisoom:** None. **J.M. Holub:** None. **R.A. Colvin:** None.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

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Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Fondo per gli Investimenti della Ricerca di Base (FIRB) program project (grant number RBAP11FRE9_001 to GL) from Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR), Italy

Title: Copper binding regulates cellular prion protein function

Authors: *X. T. NGUYEN[1], H. T. TRAN[1], D. COJOC[2], G. LEGNAME[1]
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Abstract: The cellular prion protein (PrP^C), mainly known for its role in neurodegenerative diseases, is involved in several physiological processes including neuritogenesis. By combining genomic approaches, different cellular assays and a novel focal stimulation technique, we have explored the molecular mechanism underlining its function as a signaling molecule in neuritogenesis. Different recombinant mutant prion proteins are obtained to treat the primary hippocampal cultures or exposed near the hippocampal growth cones (GC) in a local stimulation manner. While focal stimulation of GC with wild-type recombinant PrP (recPrP) induced neurite outgrowth and rapid GC turning towards the source, N-terminal mutants fail to support this

function.
In particular, the copper-binding sites mutants present at the N-terminus of PrP^C are toxic to neurons indicating this region being crucial for the function of the protein. Mutants of recPrP including a key mutation for prion conversion H95Y (Giachin, Mai et al. 2015) or the GSS-linked mutation abolish the function on neuritogenesis. Altogether, our findings indicate the functional regions for PrP^C in neuritogenesis and suggest a potential link between loss-of-function of the protein and disease initiation.

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Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

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Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: BBSRC grant SG4208

Title: *In vivo* imaging of mitochondrial transport deficits in the rTg4510 mouse model of tauopathy

Authors: *J. D. JOHNSON[1], R. M. LEES[1], J. S. JACKSON[2], M. J. ONEILL[3], M. C. ASHBY[1]
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Abstract: The pathological accumulation of tau is associated with a number of diseases including Alzheimer's Disease (AD). Tau is predominantly a microtubule stabilizing protein, enabling the replenishment and regulation of the key transport route for axonal cargoes. Tau can become hyperphosphorylated, becoming aggregative and toxic, spreading throughout the brain forming intracellular neurofibrillary tangles. Uncovering the functional elements that could underpin the synapse loss and cell death observed in tauopathies is crucial in slowing down or reversing these diseases. Mitochondria are crucial for neuronal health and maintenance of synaptic function, and have been linked to degenerative pathologies. Mitochondrial dysfunction can lead to changes in ATP production, Reactive Oxygen Species deregulation, disruption in calcium buffering and apoptosis control. These dysfunctional pathways can lead to synaptic damage and cell death. The changes and the time course of mitochondrial function and its relationship to synapse loss in tauopathies, AD patients and animal models is not well known. Here, longitudinal in vivo two-photon microscopy is performed in rTg4510 mice, which express a repressible form of human tau containing the potent P301L mutation. rTg4510 mice and control littermates were transduced with an AAV driving expression of cytosolic & mitochondrial-targeted fluorescent proteins in a subset of excitatory cortical neurons. Repeated

imaging of the distribution and motility dynamics of axonal mitochondria was performed in head-fixed, anaesthetized mice. These results show the changes in mitochondria occurring with increasing tau pathology. Transgenic mice show decreased chances of motility and in the ratio of motile mitochondria vs total mitochondria. An initial increase in mitochondrial density along the axon is seen in the rTG4510 mice, followed by a decrease against control mice. An increase the pause ratio of the mobile mitochondria is seen along with an increase in the average pause time. Age related decreases mobile mitochondria speed are also seen in the rTg4510 mice. The data indicates mitochondria may have a key role in the tau related neurodegeneration from an early age.

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677. Tauopathies, Tau-Dementias, and Prion Diseases II

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 677.13/BB24

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Optimization of structure-based tau aggregation inhibitors

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Abstract: Although the cause of Alzheimer's disease (AD) is not known, the aggregation of tau is believed to be a key step in the pathobiology of AD. Disease severity, cognitive dysfunction, and neuronal cell death are correlated with the presence of neurofibrillary tangles, which are composed of aggregated tau. Approaches to design tau aggregation inhibitors (TAIs), however, have been hampered by the lack of structural understanding of these toxic aggregates. To enable the in silico structure-based design of Tau aggregation inhibitors detailed atomic structures and computational models that identify the domains within Tau that drive aggregation have been developed (Sawaya et al. 2007, Colletier et al. 2011, Thompson et al. 2005, Laganowsky et al. 2012, Goldschmidt et al. 2010). Two small protein segments ^{306}VQIVYK^{311} and ^{275}VQIINK^{280} have been proven to be responsible for tau aggregation both *in vitro* and *in vivo*, and modulate its toxicity. The atomic structure of VQIVYK has been determined and, with the use of Rosetta computational design software, a series of peptide inhibitors of tau fiber formation were designed. Natural and non-natural amino acid containing peptides have served as starting points for the further optimization of inhibitors. High-throughput biochemical assays have been used to screen libraries of TAIs synthesized to increase the potency and selectivity of the original warheads. The ability of TAIs to block aggregation of full length and mutated tau isoforms,

containing both the VQIVYK and VQIINK amyloidogenic repeats, have been used to confirm the mechanism of action of these inhibitors. Data will be shown that also demonstrates cellular disruption of Tau aggregation by these TAIs using a luciferase-based reporter assay. In summary, potent Tau aggregation inhibitors have been designed utilizing a structure-based model of Tau aggregation that are now being evaluated for *in vivo* efficacy in mouse models of Tau-induced neurodegeneration.

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Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

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Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

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UPMC SPRIG Initiative Pilot Grant

Title: Impaired autophagy exacerbates neurotoxicity induced by general anesthetics in a culture model of familial Alzheimer's disease

Authors: C. WARD[1], M. YANG[2,4], Y. WANG[2,5], G. LIANG[2], Z. XU[2,6], *C. T. CHU[7], H. WEI[3]
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Jinan, China; [6]Tongji Univ. Sch. of Med., Shanghai, China; [7]Div. of Neuropathology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: General anesthetics have been shown to worsen pathology and cognitive dysfunction in Alzheimer's disease animal models, but the mechanisms remain unclear. Our previous work suggests that isoflurane causes neurotoxicity in a culture model of familial Alzheimer Disease (FAD) through abnormal calcium release from the endoplasmic reticulum (ER). We hypothesize that the general anesthetic propofol induces cell death through disruption of intracellular calcium homeostasis and dysregulation of lysosome and autophagy function in Alzheimer's disease.
PC12 cells stably transfected with wild type (WT) or mutated presenilin-1 (L286V) were treated with different concentrations of propofol for 6 or 12 hr. The effects on cell survival, cytosolic calcium concentration ($[Ca^{2+}]_c$) and autophagy induction and flux were investigated. The stable and sensitive Cell Counting Kit-8 (Sigma) was employed to measure cell viability. Changes in $[Ca^{2+}]_c$ were determined by Fura-2 AM dye. We evaluated $[Ca^{2+}]_c$ after exposing both cell lines to propofol in the presence or absence of the ryanodine receptor (RYR) antagonist (dantrolene), the inositol 1,4,5-trisphosphate ($InsP_3$) receptor antagonist, (xestospongin C, Xc), and intracellular calcium chelator (BAPTA-AM). We used LysoTracker probes to determine the effects on lysosome acidification in WT and L286V cells. V-ATPase localization to the lysosome or ER was determined by immunofluorescence.
Propofol dose- and time- dependently induced cytotoxicity in both L286V and WT PC12 cells, while bafilomycin, an inhibitor of autophagy flux, significantly aggravated the propofol-mediated cell death in L286V but not WT cells. BAPTA-AM, dantrolene and Xc significantly inhibited propofol-induced elevation of $[Ca^{2+}]_c$ and cell damage. However, combined use of dantrolene and Xc, paradoxically and abnormally increased $[Ca^{2+}]_c$ by calcium influx from the extracellular space and potentiated propofol induced cell damage. Compared to WT cells, L286V cells demonstrated significantly reduced lysosome acidification. The effects of RYR- or $InsP_3$-antagonists on anesthetic effects on autophagic flux and on ER and lysosomal distribution of V-ATPase were studied.
Our results suggest that autophagy plays an important role in regulating cell death induced by the general anesthetic propofol in a culture model of FAD, and highlight the importance of understanding how excessive calcium release from the ER mediated by RYR or $InsP^3R$ impact different stages of autophagy.

Disclosures: C. Ward: None. **M. Yang:** None. **Y. Wang:** None. **G. Liang:** None. **Z. Xu:** None. **C.T. Chu:** None. **H. Wei:** F. Consulting Fees (e.g., advisory boards); Eagle Pharmaceutical Company, New Jersey, USA, Well Lead Medical Company, Guangzhou, China.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 677.15/BB26

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant RO1 GM084979

Title: Atg-5 plays important role on propofol regulation of autophagy and cell survival

Authors: *H. WEI[1], Z. XU[3], Y. WANG[4], G. LIANG[2], Z. LIU[6], W. MA[5], C. WARD[7]
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Abstract: In fibroblasts with total knock out of Atg 5 ($ATG5^{-/-}$), a key regulator on autophagy activity, we studied the role of Atg5 on the effects of propofol on autophagy and cell proliferation and survival. Cell viability and death were measured by MTT reduction and lactate dehydrogenase (LDH) release assays respectively. Cell proliferation was determined by Bromodeoxyuridine incorporation. Autophagy activity was determined by measuring changes of LC3 II protein levels in the presence or absence of Bafilamycin. The cytosolic calcium concentrations ($[Ca^{2+}]_c$ were measured using dye Fura-2, in the presence or absence of xestospongin C or dantrolene. Propofol dose-, time- and Atg5-dependently affected cell proliferation and death. Propofol at 200 µM for 6 or 12 hours did not affect cell viability in either type of cells. However, a 24 hour treatment of propofol at 10 µM significantly increased MTT. Propofol at 200 µM decreased MTT in the $ATG5^{-/-}$ but not WT cells. Propofol at 100 and 200 µM induced cell death more significantly in $ATG5^{-/-}$ cells. Dantrolene or Xc significantly worsen or inhibited propofol-induced cell death in WT or $ATG5^{-/-}$ deficient cells respectively. Furthermore, propofol at 10 µM significantly increased proliferation, while propofol at 200 µM significantly decreased cell proliferation only in $ATG5^{-/-}$cells. Propofol dose-dependently increased the autophagy biomarker LC3 II and was potentiated by bafilamycin, only in WT but not $ATG5^{-/-}$ cells. Propofol increased $[Ca^{2+}]_c$ in both types of cells, but significantly more in $ATG5^{-/-}$ cells, which could be inhibited significantly by dantrolene or Xc. Propofol causes Ca^{2+} release from the endoplasmic reticulum via $InsP_3$ and or ryanodine receptors more dramatically in $ATG5^{-/-}$ then WT cells. Propofol promotes or suppresses cell proliferation at low and clinically relevant or high pharmacological concentrations respectively in an Atg5-dependent manner. Propofol induced cell death only at high pharmacological concentrations more significantly in $ATG5^{-/-}$ than WT cells. This study suggests that Atg5 plays a crucial role in propofol regulation of autophagy and associated cell survival and proliferation via differential activation of $InsP_3R$ or RYR.

Disclosures: **H. Wei:** F. Consulting Fees (e.g., advisory boards); advisory boards. **Z. Xu:** None. **Y. Wang:** None. **G. Liang:** None. **Z. liu:** None. **W. Ma:** None. **C. Ward:** None.

Poster

677. Tauopathies, Tau-Dementias, and Prion Diseases II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 677.16/BB27

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant GM58055

Title: Isoflurane inhibition of exocytosis coupled to P/Q- and N-type voltage-gated Ca^{2+} channels

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Abstract: The general anesthetic ether isoflurane inhibits voltage-gated Na^+ channels, which results in reduced Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCCs) at synaptic terminals and suppression of synaptic vesicle (SV) exocytosis. It remains unclear what contribution direct inhibition of presynaptic VGCCs by isoflurane makes to the reduced SV exocytosis observed in central nervous system nerve terminals. We used the calcium sensitive dye, Magnesium Green, together with the red-shifted reporter of vesicle recycling mOrange2 coupled to the vesicular glutamate transporter vGLUT1 to quantitate Ca^{2+} influx and SV exocytosis by live-cell imaging of rat hippocampal neurons. Using real-time imaging of both reporters loaded/expressed in the same neurons, we tested isoflurane effects on Ca^{2+} influx and SV exocytosis. The selective VGCC blockers conotoxin-GVIA and agatoxin-IVA were used to isolate P/Q- and N-type VGCC effects, respectively. In the presence of 1 μM conotoxin-GVIA, 2MAC isoflurane inhibited 50 mM KCl evoked Ca^{2+} influx (by 58 ± 9%; n = 13, $P < 0.01$, paired *t*-test) and SV exocytosis (by 51 ± 7%; n = 13, $P < 0.001$). In the presence of 400 nM agatoxin-IVA, Ca^{2+} influx and SV exocytosis were inhibited by isoflurane by 72 ± 8% (n = 13, $P < 0.01$) and 71 ± 7% (n = 13, $P < 0.001$), respectively. Isoflurane inhibited Ca^{2+} influx and SV exocytosis mediated by P/Q-type VGCC more than by N-type VGCC. These results suggest that isoflurane also reduces Ca^{2+} influx in a voltage-gated Na^+ channel independent manner to suppress SV exocytosis. Together with previous findings showing cell type dependent VGCC expression, VGCC subtype-selective inhibition might contribute to cell type-specific modulation of SV exocytosis by volatile anesthetics.

Disclosures: Y. Koyanagi: None. **Z. Zhou:** None. **H.C. Hemmings:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.01/CC1

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Tau Consortium/Rainwater Foundation

NIH Grant R01-NS060885

NIA Grant P01AG014930

National Parkinson Foundation CSRA Chapter

Par fore Parkinson

Title: Benfotiamine treatment activates the Nrf2/ARE pathway and is potently neuroprotective in a transgenic mouse model of tauopathy

Authors: *V. TAPIAS[1], S. JAINUDDIN[1], M. AHUJA[2], C. STACK[1], C. ELIPENAHLI[1], J. VIGNISSE[3], M. GERGES[1], N. STARKOVA[1], H. XU[1,2], A. A. STARKOV[1], L. BETTENDORFF[3], D. M. HUSHPULIAN[4,5], *N. A. SMIRNOVA[4], *I. G. GAZARYAN[6,7], N. A. KAIDERY[2], S. WAKADE[2], N. Y. CALINGASAN[1], B. THOMAS[2], G. E. GIBSON[8,1], M. DUMONT[1], M. F. BEAL[1]
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Abstract: Impaired glucose metabolism, decreased levels of thiamine (vitamin B1) and its phosphate esters, and downregulated activity of thiamine-dependent enzymes, such as pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and transketolase have been linked to Alzheimer's disease (AD). Thiamine-deficient mice exhibit increased amyloid deposition, tau hyperphosphorylation, and oxidative damage**[1]**. Experimental evidence has shown that benfotiamine (BFT), a synthetic S-acyl derivative of thiamine, rescued cognitive deficits and reduced amyloid burden in APP/PS1 mice**[2]**. We investigated whether BFT confers neuroprotection against tau phosphorylation and the generation of neurofibrillary tangles (NFTs) – which causes frontotemporal dementia in humans – in a mouse model of tauopathy. Exposure to BFT resulted in increased lifespan, behavioral improvement, reduced and glycated tau and

NFTs, and prevented neuronal death in P301S transgenic (TG) mice. In addition, BFT administration significantly ameliorated mitochondrial dysfunction, attenuated oxidative damage, and decreased the expression of several proinflammatory mediators, consistent with a possible activation of the Nrf2/ARE neuroprotective pathway. Accordingly, we found that BFT (but not thiamine) triggers the expression of Nrf2/ARE-dependent genes in wild-type (WT) but not in Nrf2-deficient fibroblasts. Our findings suggest that BFT is a promising therapeutic agent for the treatment of tauopathies.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.02/CC2

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Sex differences in the microRNA-mediated regulation of microglia function in a mouse model of Alzheimer's Disease

Authors: *L. KODAMA[1], J. I. ETCHEGARAY[2], Y. ZHOU[2], E. GUZMAN[3], K. S. KOSIK[4], L. GAN[5]
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Abstract: MicroRNAs are a class of small non-coding RNAs that suppress translation of their mRNA targets and have been implicated in modulating gene expression of immune cells. Recent studies have found miRNAs are also important in the regulation of the innate immune system of the central nervous system, namely in controlling microglia function. Dysregulation of microglia function is seen in many CNS pathologies, including tauopathies such as Alzheimer's Disease (AD), but how microglial miRNAs play a role in tau pathology is not known. In this study, we show that downregulating microglial microRNAs by conditionally floxing out dicer specifically in microglia (Cx3cr1Cre-ERT2/+; DicerF/F) exacerbates tau burden in male P301S (PS19) AD mice but not in female mice at 8 months of age. Pathology is especially increased in the entorhinal cortex region. To study the underlying sex differences and miRNA regulation of microglia function, we analyzed microglia density and morphology. Cx3cr1Cre-ERT2/+; DicerF/F male and female mice both show a decrease in microglia density but do not seem have

a defect in proliferative response to aggregated tau. Morphological analysis, however, shows female but not male Cx3cr1Cre-ERT2/+; DicerF/F mice have microglia with shortened processes and larger cell bodies, reminiscent of activated cells. We also did RNA sequencing specifically for miRNAs isolated from control and PS19 adult microglia to better understand the expression profile and functional changes in PS19 mice. Preliminary results show differential expression of several miRNAs, including upregulation of miR155 involved in the proinflammatory response pathway, and miR380-5p involved in apoptosis. Together, these data provide an entry point to further characterize the role of gender and miRNA in regulating microglia function and how microglia may be involved in sexual dimorphic neurodegenerative phenotypes.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.03/CC3

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Michael J. Fox Foundation for Parkinson's Research

Title: Protein phosphatase 2A is dysregulated in tauopathies of progressive supranuclear palsy and alzheimer's disease

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Abstract: Abnormal aggregates of hyper-phosphorylated tau are a characteristic feature of several neurodegenerative disorders including Progressive Supranuclear Palsy (PSP) and Alzheimer's disease (AD), but factors contributing to this pathologic tau phosphorylation are not well understood. In the present investigation, we studied the regulation of the phosphatase responsible for dephosphorylating tau in the brains of patients with PSP and AD. Protein phosphatase 2A (PP2A), which is a family of conserved enzymes that constitute the majority of serine/threonine phosphatase activity in the brain, is a holoenzyme composed of a catalytic C subunit, a scaffold-like A subunit, and one of several regulatory B subunits that confer substrate specificity. The major tau phosphatase is B55α subunit-containing PP2A, the assembly and activity of which are regulated by reversible carboxyl methylation of the C subunit. In AD brains, reduction in PP2A methylation and PP2A phosphatase activity, as well as decreases in

B55α containing holoenzyme and PP2A methylation methylating enzyme have been noted. HoweverHere, we sought to address whether those findings relate to tau pathology or to the prominent concomitant amyloid pathology of AD by comparing them in the relatively pure tauopathy PSP. The state of PP2A methylation, as well as the expression of its methylating enzyme, leucine carboxyl methyltransferase (LCMT-1), and demethylating enzyme, protein phosphatase methylesterase (PME-1), were studied in the frontal cortex of postmortem brains from PSP and AD cases as well as age-matched non-neurological controls using immunohistochemical stains. Results showed that methyl-PP2A is reduced, particularly in AD brains, while demethyl-PP2A is increased, with no changes in total PP2A or B55α subunit, resulting in a reduction in the ratio between methyl/demethyl PP2A of 63% in PSP and 75% in AD compared to controls. This is associated with a significant decrease in LCMT-1 expression, and a two-fold increase in PME-1 in both PSP and AD brains. These findings suggest that PP2A dysregulation in tauopathies may contribute to the accumulation of hyper-phosphorylated tau and to neurodegeneration, raising the possibility that boosting PP2A phosphatase activity may be a disease modifying therapeutic strategy for these disorders.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.04/CC4

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Alzheimer's Association Grant 453589

NIH/NINDS Grant NS079374-02

Title: Dysregulation of Fgf14 by the tau transgene array is required for neurodegeneration in the rTg4510 mouse model of tauopathy

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Abstract: Tauopathies such as Alzheimer’s disease are neurodegenerative diseases in which the microtubule-associated protein tau (MAPT) is abnormally regulated. The rTg4510 mouse model, which harbors a tau transgene with a mutation known to cause tauopathy (P301L), is one of the most widely used models of these diseases. These mice recapitulate key features of human

disease in that they develop neurofibrillary tangles, experience cognitive deficits, and exhibit dramatic loss of neurons. This model was conventionally made using pronuclear injection, resulting in random integration of the transgene into the mouse genome. We have now generated a precision-engineered equivalent of the rTg4510 line in which a single copy of the same tau transgene cassette is integrated into a predetermined, intergenic locus (T2/T2). Although this precision-engineered line expresses even more human tau than rTg4510, we found that these mice do not exhibit any significant loss of neurons, and therefore performed whole-genome sequencing analyses of rTg4510 mice to determine the underlying cause of neuron loss in this transgenic model. We found that approximately 70 tau transgene copies replaces a 244 kb segment of chromosome 14, resulting in a deletion of the first exons and promoter regions of the longer variants of the fibroblast growth factor 14 (Fgf14) gene (splice variants V2, X1, and X2). Only the shortest variant of the Fgf14 gene (V1) remains intact. We measured Fgf14 mRNA expression levels of these splice variants in rTg4510 brains and found that the V2, X1, and X2 levels were decreased, while expression levels of V1 were dramatically increased in comparison to non-transgenic controls. Disruption of the FGF14 gene has been linked to a range of neurological abnormalities, including microcephaly, and the dysregulation of this gene in rTg4510 mice is likely to make a significant and perhaps even primary contribution to the cognitive deficits and neuron loss that develop in these mice as they age. In light of these findings, we believe that it is critical to reevaluate all studies using the rTg4510 model, and encourage the use of models made using precise transgene targeting for any future animal studies to avoid similar confounds that may impede the development of disease-modifying treatments.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.05/CC5

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Deciphering HDAC6 interaction with human Tau using zebrafish

Authors: N. RIBEIRO PALHA[1], C. QUEVEDO[2], *A. DEKEYNE[1], B. PUVION[1], A. MURIANA[2], A. AZUALDE[2], C. LOUIS[1], J. P. KISS[1]
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Abstract: HDAC6 is a Zn^{2+}-dependent class IIb lysine deacetylase which deacetylates and regulates cytoplasmic non-histone proteins (e.g. α-tubuline, cortactin, HSP90). In neurons, HDAC6 might play a role for their integrity and survival *via* activation of proteostatic mechanisms and inhibition of toxic downstream events (apoptosis, Tau oligomerization,

microtubule destruction) (d'Ydewalle et al., 2012, *Traffic* 13:771-779). In Alzheimer's disease (AD) patients, it has been shown that Tau binds and inhibits deacetylase activity of HDAC6, as revealed by hyperacetylation of α-tubulin (Perez et al., 2009, *J Neurochem* 109:1756-66). On the other hand, the protein level of HDAC6 in AD brains – although functionally impaired - is increased compared to normal brain (Ding et al., 2008, *J Neurochem* 106:2119-30). The assumption then is that α-tubulin is hyperacetylated in AD patients because Tau binds and inhibits the activity of HDAC6. Therefore, disrupting the interaction between Tau and HDAC6 in order to restore its activity could be of therapeutic interest.
Here we report a characterization of the functional link between Tau and HDAC6 in zebrafish (zf) larvae. *First*, the conserved role of zfHDAC6 in tubulin deacetylation was verified by western blot using either pharmacological (SAHA and tubastatine A) or genetic (morpholino-mediated knockdown) inhibition of zfHDAC6. Furthermore, overexpression of human HDAC6 decreased the acetylation of zebrafish α-tubulin. *Second*, co-immunoprecipitation data suggests that zfHDAC6 interacts *in vivo* with human Tau in transgenic zfTAUP301L larvae, a zebrafish tauopathy model (Paquet et al., 2009, *J Clin invest* 119:1382-95). Interestingly, experimental data from human cell lines and cell-free assays also supported a physical interaction between these two proteins. *Third*, zfHDAC6 morpholino-induced knockdown did not modify tau pathology phenotypes displayed by this transgenic line, namely neuronal cell death and shortened motoneuron axonal extensions. *Finally*, pharmacological inhibition of HDAC6 in tauopathy fish did not modify axonal length defects and - not in line with the working hypothesis - *rescued* neuronal death. As such, our zebrafish results do not support a role for HDAC6 in modulation of tau pathology, in line with recent data from human AD brain samples also pointing to an absence of any functional link between AD pathology and HDAC6 dysfunction. Together, our data illustrates how the zebrafish model organism can play an important role in proteinopathy drug discovery programs.

Disclosures: **N. Ribeiro Palha:** A. Employment/Salary (full or part-time):; Institut de recherches Servier. **C. Quevedo:** A. Employment/Salary (full or part-time):; Biobide. **A. Dekeyne:** A. Employment/Salary (full or part-time):; Institut de Recherches servier. **B. Puvion:** A. Employment/Salary (full or part-time):; Institut de Recherches servier. **A. Muriana:** A. Employment/Salary (full or part-time):; Biobide. **A. Azualde:** A. Employment/Salary (full or part-time):; Biobide. **C. Louis:** A. Employment/Salary (full or part-time):; Institut de Recherches servier. **J.P. Kiss:** A. Employment/Salary (full or part-time):; Institut de Recherches servier.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.06/CC6

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: CEA MIRCen

Title: Study of the astrocyte-neuron relationship in a novel gene transfer-based rodent model of tauopathy

Authors: *K. CAMBON, A. MATÉ DE GÉRANDO, M. D'ORANGE, G. LIOT, L. STIMMER, G. AURÉGAN, C. JOSÉPHINE, M.-C. GAILLARD, E. BROUILLET, P. HANTRAYE, A.-P. BEMELMANS
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Abstract: Tauopathies are neurodegenerative diseases characterized by the aggregation of Tau protein. These pathologies exhibit a wide variety of clinical and anatomo-pathological presentations, which may result from different pathological mechanisms. While in Alzheimer's disease it is essentially neurons which accumulate fibrillary tangles, glial inclusions in the shape of astrocytic plaques or tufted astrocytes are also observed in corticobasal degeneration and progressive supranuclear palsy respectively. However, to date, the mechanisms leading to the presence of tau aggregates in astrocytes have been little investigated. Furthermore, the functional consequences of such astroglial tauopathies are still unclear. Our aim was to study the relationship between neurons bearing soluble and/or aggregated Tau species and their neighboring astrocytes. To that purpose, we generated a fast-developing model of tauopathy in rodents by injecting adeno-associated viral vectors (AAV) encoding the human 1N4R Tau isoform in the hippocampus of adult rats and mice. At one month post-injection, overexpression of P301L mutant-Tau or of a pro-aggregating vector lead to the formation of AT100- and AT8-positive aggregates not only in neurons but also in astrocytes. In situ hybridization showed that most Tau positive- astrocytes were not transduced by the vectors, suggesting that astroglial tauopathy was secondary to the presence of neurofibrillary tangles. In order to better understand this effect, we will use co-cultures of neurons and astrocytes to determine whether astrocytes are able to take up aggregates either released from neurons or from phagocytosis of tangle-bearing neurons. The functional consequences of exposure to neurofibrillary tangles on astrocytic functions will also be evaluated.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.07/CC7

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Brain/MINDS

Title: Silencing of FUS in the non-human primate brain via stereotaxic injection of an adeno-associated virus encoding shRNA

Authors: *K. ENDO, S. ISHIGAKI, Y. FUJIOKA, H. WATANABE, M. KATSUNO, G. SOBUE
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Abstract: Frontotemporal lobar degeneration (FTLD) is one of the devastating dementia syndromes which show an abnormality in social cognition or social behavior. FUS, an RNA binding protein has been identified as a causative molecule which is dislocated from the nucleus to the cytoplasm in the affected neurons of FTLD or amyotrophic sclerosis (ALS). Based on the hypothesis that aberrant RNA metabolism could be one of the major causes for the diseases, we have shown that the FUS-silencing in the hippocampus of mice could be a good candidate animal model for FTLD. However, due to the limitations to study social abnormalities in rodents, it would be desirable to establish a non-human primate model of FTLD. For this purpose, we established FUS-silencing method using stereotaxic injection of AAV to non-human primate (Callithrix jacchus). We designed shRNAs against marmoset FUS gene and generated AAV9 virus encoding the most effective shRNA against FUS (shFUS). The AAV encoding shFUS (AAV-shFUS) was injected into the frontal cortex or caudate of a young adult marmoset, whereas AAV encoding control shRNA was injected into the contralateral side. We obtained approximately 80% of silencing of FUS by the injection of AAV-shFUS. These techniques would enable us to establish a non-human primate model of FUS-silencing in various brain tissues for investigating the pathomechanism of FTLD.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.08/CC8

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Creating a *Drosophila melanogaster* model of prion-like tau protein spread

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Abstract: Tauopathies are a class of neurodegenerative diseases pathologically characterized by the accumulation of fibrillar tau protein aggregates. In Alzheimer’s disease, the most prevalent

tauopathy, these aggregates form neurofibrillary tangles, one of the major pathological hallmarks of the disease. Strikingly, tau pathology propagates hierarchically over time and appears to spread along the brain circuitry. In recent years, an increasing amount of evidence has surfaced to support the hypothesis of a prion-like mechanism for tau spread. Tau is now known to spread between cells and form a variety of stably transmitted strains *in vitro* as well as *in vivo*. The cellular mechanisms mediating and regulating tau spread have not been well characterized. Here, we propose to create a *Drosophila melanogaster* model of the prion-like spread of pathogenic tau. This model will provide a tool to study the processes involved in prion-like tau propagation in a short-lived, cost-effective animal model for which a wide variety of genetic tools are available. We will make use of the well-described circuitry of the *Drosophila* olfactory system, part of which consists of output neurons in the mushroom body projecting to five target regions. Based on this circuitry, a two-pronged approach will be employed to model the two key features of prion-like protein transmission: 1) spreading of tau to other cell populations and 2) a capacity to recruit native tau to seed aggregation. A split-Gal4 system will direct expression of tau^{R406W}, a tau mutant associated with familial tauopathy, to a small subset of mushroom body output neurons. The spread of tau beyond the neurons where it is expressed will be assessed by immunofluorescence. To detect the capacity of tau seeds to spread to synaptically connected regions and seed aggregation of tau in downstream neurons, the same split-Gal4 system will be used to express tau^{R406W}-CFP in mushroom body output neurons, while a LexA system will drive tau^{WT}-YFP expression in the target regions. CFP-labeled tau spreading along neuronal projections and recruiting the local YFP-tagged tau to seed aggregation in target regions will emit a FRET signal. A *Drosophila* model of tau spread will allow us to investigate the mechanisms controlling this phenomenon in adult brains, with the long-term goal of developing treatment strategies targeting the prion-like spread of pathogenic tau protein. In this context, a FRET-based model of tau seeding is well suited for screening of genetic and pharmacological interventions that interfere with putative transmission mechanisms.

Disclosures: S.A. Levy: None. **B. Frost:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.09/CC9

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NRF-2016R1D1A1B02011328

HI16C0965

Title: Proteinase K-resistant proteins linked with the different types of advanced glycation end products in the 263K prion-infected brain

Authors: *Y.-G. CHOI[1], J.-I. KIM[2], E.-K. CHOI[1], J. CASTILLA[3,4], Y.-S. KIM[1,5]
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Abstract: In the previous studies it was shown that advanced glycation end product (AGE) is linked into the N-terminus of pathogenic prion isoform (PrP^{Sc}), probably at one or more of the three Lys residues (23, 24 and 27) on its N-terminus, and that the linked AGE type into the pathogenic prion isoform is N^{ε}-(carboxymethyl)lysine (CML), which is a major AGE form specific to Lys residue produced by nonenzymatic glycation. In this study, we investigated whether the other types of AGEs are linked into the pathogenic prion isoform, and whether there are the AGE-linked pathogenic prion isoforms in the brains of some transgenic mice with transgened PrP. The insoluble fractions that PrP^{Sc} could be enriched were isolated in the brains of 263K-infected hamster, 139A scrapie prion-infected mice (C57BL and tga20), PrP KO mouse and bank vole PrP^{109I} tg mouse. R3 anti-AGEs, anti-pentosidine, anti-pyrraline, anti-CML, anti-N^{ω}-(carboxymethyl)arginine (CMA), and 3F10 anti-PrP antibodies were used. As reported in the previous studies, AGE was linked into the pathogenic prion isoform in the 263K scrapie prion-infected hamster brain. Among the known AGE types, it was identified that pentosidine, pyrraline, and CMA which is a CML analogue as well as CML were linked into the proteinase K (PK)-resistant proteins, which might be the pathogenic prion isoforms because there would be only the PK-resistant pathogenic prion isoforms in the insoluble fraction isolated from the infected brain following PK digestion. As the different types of AGEs-linked proteins were detected even after PK digestion, the position of the different types of AGE linkage would be the C-terminal position of the pathogenic prion isoform (PrP90-231 of 263K scrapie prion isoforms) if the PK-resistant proteins were the pathogenic prion isoforms. In addition, the pathogenic prion isoforms both in the 139A scrapie prion-inoculated tga20 mice and in the bank vole PrP^{109I} tg mice are also linked with one or more of the AGEs types. The AGE linkage into the pathogenic prion isoforms in the brains of the PrP transgened mouse models was not dependent on their glycosylated types, as observed in the brains of 263K-infected hamster and 139A-infected C57BL mouse. Although it failed to show that the different types of AGE-linked PK-resistant proteins are the pathogenic prion isoforms by immunoprecipitation analysis, it is suggested that some of PrP^{Sc} isoforms would be post-translationally modified with the different types of AGEs in the pathologically affected brains (2016R1D1A1B02011328; HI16C0965).

Disclosures: Y. Choi: None. **J. Kim:** None. **E. Choi:** None. **J. Castilla:** None. **Y. Kim:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.10/CC10

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH grant NS090993

Title: The expression of the neurotoxic tau45-230 fragment leads to changes in the cytoskeleton associated with defects in neurite elongation and synapse formation in hippocampal neurons

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Abstract: We have shown that tau_{45-230} induces neurodegeneration followed by cell death in the context of AD and related disorders. In addition, our previous results indicated that a subset of tau_{45-230} was associated with the cytoskeleton of hippocampal neurons. In the present study, we assessed whether this subcellular localization could underlie the neurotoxicity of this tau fragment. To identify tau_{45-230} effects on the cytoskeleton, we determined the composition of the microtubular system as well as the monomeric to filamentous actin ratio in: 1- cultured hippocampal neurons obtained from embryonic day 16 (E16) pregnant wild type mice transfected with tau_{45-230}-GFP; 2- cultured hippocampal neurons obtained from E16 transgenic tau_{45-230} pregnant mice; and 3- wild type and transgenic tau_{45-230} hippocampal neurons that develop *in situ* (postnatal month 3 to 9). Untransfected cultured hippocampal neurons obtained from E16 wild type mice were used as additional controls. These experiments were performed by means of quantitative Western blot and immunocytochemistry analyses. Our results showed that the expression of tau_{45-230} in hippocampal neurons that develop either *in situ* or in culture induced a transient increase of tyrosinated tubulin, a marker of unstable microtubules. Furthermore, the presence of this neurotoxic tau fragment was associated with a significant reduction in actin filaments under these experimental conditions. These changes in the composition of microtubules have been correlated with decreased elongation and maintenance of axons and dendrites in central neurons. On the other hand, decrease in actin filaments has been associated with altered growth cone motility and synapse formation in hippocampal neurons. Together, these results suggest that tau_{45-230} could exert its toxic effects, at least in part, by modifying the composition of the neuronal cytoskeleton, and in turn, inducing neurite degeneration and synapse loss in AD and other neurodegenerative diseases. *This work was supported by NIH grant NS090993 to AF.*

Disclosures: **A.B. Ferreira:** None. **S. Afreen:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.11/CC11

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Wanda Simone Endowment Fund for Neuroscience

Alzheimer Art Quilt Initiative

Title: The Role of 5-lipoxygenase on tau pathology, synaptic integrity, and cognition in a mouse model of tauopathy

Authors: *A. VAGNOZZI[1], P. F. GIANNOPOULOS[2], D. PRATICO[1]
[1]Lewis Katz Sch. of Med. At Temple Univ., Philadelphia, PA; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Neurodegenerative tauopathies are characterized by pathological accumulation of highly phosphorylated isoforms of tau protein, which leads to progressive neuronal loss. Neuroinflammation often accompanies these diseases; however, the direct role of neuroinflammation in tauopathies remains unknown. 5-lipoxygenase (5LO) is a pro-inflammatory enzyme, which produces several bioactive metabolites and is widely expressed in the central nervous system. Previously, our group showed that 5LO modulates the Alzheimer's disease (AD) phenotype of APP transgenic mice as well as a mouse model with plaques and tangles. However, whether this protein modulates tau phosphorylation and subsequent pathology independently from its effect on APP metabolism remains to be fully investigated. In the current study, we provide evidence for an age-dependent and region-specific upregulation of the 5LO pathway in a transgenic mouse model of tauopathy, the P301S line. In addition, we demonstrate that genetic deletion of 5LO in this mouse model results in significant memory improvement, reduces tau phosphorylation at specific epitopes, and rescues synaptic pathology and neuroinflammation. In vitro studies confirm that 5LO directly modulates tau phosphorylation at the same epitopes as in brain tissues. Taken together, our data reveal an active involvement of the 5LO pathway in the development of the tauopathy phenotype and provide strong support to the hypothesis that this enzymatic protein should be considered a novel and viable therapeutic target for the treatment of human tauopathy.

Disclosures: A. Vagnozzi: None. **P.F. Giannopoulos:** None. **D. Pratico:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.12/CC12

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: 5K12GM111726-02

Title: Investigating the effects of nuclear calcium signaling in the pathogenesis of tauopathies

Authors: *R. E. MAHONEY, M. GAMEZ, B. FROST
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Abstract: Calcium is required for the function of all cells in the body, including neurons. The pivotal role of calcium in so many neuronal processes dictates the need for precise regulation of its intracellular levels. Any dysregulation, however subtle, could lead to dramatic changes in normal neuronal function. For example, during adaptive processes such as learning and development, changes in transmembrane calcium fluxes correlate with changes in neuronal excitability and structural connectivity. Calcium thus is likely to have key roles in the cellular processes underlying aging-related changes in the brain, including normal age-associated memory impairments as well as more severe dementias, including Alzheimer's disease. Central to this question we have investigated the role of nuclear calcium in the progression of tauopathies in the fruit fly *Drosophila melanogaster*. Preliminary studies suggest that pathological tau reduces calcium levels, possibly through a decrease in the expression of the *Drosophila* BK channel homolog, *Slowpoke*, specifically within the neuron. We will further investigate tau-mediated reduction of nuclear calcium, and will determine if genetically increasing nuclear calcium along with neuronal *Slowpoke* expression alleviates tau-induced neurotoxicity, and increases healthspan and lifespan *in vivo*.

Disclosures: R.E. Mahoney: None. **M. Gamez:** None. **B. Frost:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.13/CC13

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: FONDECYT 1140968

FONDECYT 1170441

CONICYT PIA ANILLO ACT1411

Title: Genetic ablation of tau reduces oxidative damage and improves mitochondrial bioenergetics during the aging

Authors: *R. A. QUINTANILLA, C. JARA, C. TAPIA-ROJAS, E. VERGARA-HERNANDEZ
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Abstract: Mitochondrial impairment has been proposed as an important factor in cerebral aging and neurodegenerative diseases. In this context, recent studies have shown an association between mitochondrial failure and tau pathology in the brain. Tau is a protein involved in the microtubule function and also play an important role in synaptic plasticity. Important studies have shown that during aging, pathological forms of tau can be accumulated and that these tau forms may directly affect mitochondrial function with negative consequences for neurons. Therefore, we determined whether the absence of tau may prevent the mitochondrial structural and functional impairments using wild-type and knock-out tau (-/-) mice of 18 months of age. We analyzed the protein expression of principal mitochondrial dynamics regulators (Drp1, pDrp1, for mitochondrial fission and Mfn1/2, Opa1, for fusion) in hippocampal extracts obtained from these mice. Analysis of the expression levels indicated not significant differences in mitochondrial fission regulators (Mfn1/2 and Opa1) in wild-type and tau (-/-) samples. In addition, pDrp1 levels were significantly reduced in tau (-/-) hippocampal samples. Interestingly, we detected a significant reduction in Cyclophilin D (CyPD) levels in hippocampal extracts from tau (-/-) mice. This is an important observation because CyPD facilitates the activation of the mitochondrial permeability transition pore (mPTP), a structure which opening compromises the entire mitochondrial function. In addition, hippocampal extracts from tau (-/-) mice showed a reduction in protein oxidative damage, detected with the 4-HNE antibody and N-tyr, and more importantly tau (-/-) hippocampal samples showed a significant increase in total ATP levels compared to wild-type. Complementary studies in hippocampal slices showed that wild-type mice presented a reduction in mitochondrial potential levels and an increase in ROS levels compared to tau (-/-) mice, indicating that tau presence affects mitochondrial health during aging. Altogether these results indicate that pathological modifications of tau may contribute to brain aging process by affecting mitochondrial dynamics and bioenergetics.

Disclosures: R.A. Quintanilla: None. **C. Jara:** None. **C. Tapia-Rojas:** None. **E. Vergara-Hernandez:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.14/CC14

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: TargetALS

NNDS

Johns Hopkins School of Medicine

Packard Center for ALS

Title: Tau aggregation causes nucleocytoplasmic transport disruption in FTD and other tauopathies

Authors: *J. G. DAIGLE[1], B. EFTEKHARZADEH[2], B. T. HYMAN, MD,PhD[3], J. D. ROTHSTEIN[4]
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Abstract: Tau pathological aggregation is found in several neurodegenerative diseases including ALS, AD and FTD. However, the cellular pathways disrupted due to tau aggregation are poorly understood. Here, we discovered nucleocytoplasmic trafficking defects in preclinical mouse model of FTD and human postmortem tissues. Additionally, we observe similar disruptions in primary mouse neuronal cultures treated with different toxic tau species. We find that phosphorylated Tau species in the cytoplasm sequester nuclear pore complex proteins and disrupt nuclear/cytoplasmic ran gradients. Using several quantitative high resolution imaging methods we are able to detect Tau binding to the nuclear pore complex at the molecular level. Tau accumulation in the perinuclear space interferes with nucleocytoplasmic transport, likely through direct interactions of tau with Nuclear pore complex elements. We believe that abnormal nuclear transport is a key pathological even in tauopathies that may extend to many neurodegenerative diseases. Targeting this pathway could prove to be a novel strategy in developing therapeutics for neurodegeneration.

Disclosures: J.G. Daigle: None. **B. Eftekharzadeh:** None. **B.T. Hyman:** None. **J.D. Rothstein:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.15/CC15

Topic: C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Influence of hyperphosphorylated tau in the hippocampal CA1 region in tau transgenic mice

Authors: *L. MUELLER-THOMSEN[1], H. SCHRODER[2], T. SCHNEIDER[3], J. GOETZ[4], S. HUGGENBERGER[5]
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Abstract: Alzheimer's disease (AD), the most frequent form of dementia, is characterized by a significant loss of brain mass mainly in hippocampal and cortical areas. The brains of patients with AD are histopathologically characterized by two hallmark lesions: extracellular amyloid-beta containing plaques and neurofibrillary tangles (NFTs) which are hyperphosphorylated forms of intracellular microtubule-binding protein tau. Under pathological conditions there is a mislocalisation of hyperphosphorylated tau and NFTs to somatodendritic compartments and spines. There is mounting evidence that hyperphosphorylated tau species drive neuronal dysfunction and degeneration in tauopathies. The impact of the pathological modified tau protein on the functions of neuronal networks was sparsely studied so far. To investigate how hyperphosphorylated tau affects neuronal functions we examined the electrophysiological properties of hippocampal network activity of mice expressing human tau (P301L htau transgenic pR5 mice) by extracellular field potential measurements using a long time potentiation (LTP) protocol. LTP is widely accepted as a cellular mechanism underlying synaptic plasticity responsible for learning and memory. The LTP mechanism is divided into two phases: the early phase is characterized by the activation of NMDA and AMPA receptors and the resulting cation influx. The late phase is characterized by gene transcription, new protein synthesis and changes in the number of single-channel conductance of AMPA glutamate receptors in spines. Here we found a significant amplitude reduction in LTP in senescent pR5 mice in contrast to their non-transgenic littermates 10 minutes after LTP induction. These finding indicates the relationship between hyperphosphorylated tau protein within hippocampal neurons and the resulting memory deficits within the second phase of LTP. For this reason our next goal is the assessment of changes of AMPA-R conductance due to the intracellular presence of hyperphosphorylated tau.

Disclosures: L. Mueller-Thomsen: None. **H. Schroder:** None. **T. Schneider:** None. **J. Goetz:** None. **S. Huggenberger:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.16/CC16

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant T32 MH064913

NIH Grant RO1 AG033679

Title: Age-dependent changes in protein degradation are reversed by NADPH oxidase inhibition in mouse brain

Authors: *J. B. RUDEN, Q. TANG, J. L. SASKOWSKI, R. J. SASKOWSKI, P. J. SPITZLER, E. A. SCHNEIDER, L. L. DUGAN
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Abstract: Age, itself, is by far the single greatest common risk factor for chronic progressive neurodegenerative conditions, but the underlying mechanisms are not completely understood. We and others previously reported the existence of large aggregates of undigested lysosomal protein "cargo" in the brains of aged wild-type mice. This accumulation of extracellular protein aggregates and presence of lipofuscins in old brains highlight an age-dependent decrease in handling of cellular and tissue garbage. Here we show that lysosomes, labeled by LAMP-1 or Cathepsin D, are significantly larger in hippocampal pyramidal neurons and inhibitory parvalbumin interneurons in 20-month-old mice than in 5-month-old mice. Motivated by our previous finding that there was increased neuronal NADPH oxidase 2 (Nox2) expression in brains of aged wild-type mice, and by reports that superoxide derived from NADPH oxidase (Nox) impairs lysosomal protein degradation, we asked whether Nox activation could be contributing to lysosomal changes by treating mice long-term with the Nox inhibitor, apocynin (100 mg/kg/day). We found a significant improvement in lysosome function, as demonstrated by a reduction of both the number and total area of p62-positive clustered aggregates in the hippocampus. We are investigating whether lysosome enlargement has also been normalized in these mice. These data are significant because they directly link Nox activity with decrease in lysosomal clearance of material. Such decrease can lead to the accumulation of extracellular and intracellular aggregates that may promote tissue injury, local inflammation, and deposition of disease-specific proteins.

Disclosures: J.B. Ruden: None. **Q. Tang:** None. **J.L. Saskowski:** None. **R.J. Saskowski:** None. **P.J. Spitzler:** None. **E.A. Schneider:** None. **L.L. Dugan:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.17/CC17

Topic: C.01. Brain Wellness and Aging

Support: NIA P01AG026572

Title: Ovariectomy and hormone treatment modulates female brain bioenergetic function in an endocrine status dependent manner

Authors: *Z. MAO[1,2], F. YIN[2], J. YAO[2], R. BRINTION[1,2]
[1]Ctr. for Innovation in Brain Science, Dept. of Pharmacol., Univ. of Arizona, Tucson, AZ;
[2]Pharmacol. and Pharmaceut. Sci., USC, Los Angeles, CA

Abstract: The perimenopause is an aging transition unique to the female that is associated with multiple neurological symptoms. Our recent study in a rodent model of human perimenopause revealed the perimenopausal transition as a critical period characterized by a significant decline in bioenergetic and synaptic functions, that is reminiscent of early stage of Alzheimer's disease (AD). Combinations of 17β-estradiol (E2) and progestogens (P4) in varying regimens are widely used as hormone therapy for menopause-related climacteric symptoms. The present study was aimed to determine the efficacy and optimal intervention window of the E2 in combination of cyclic P4 therapy on female rat brain at different stages of the perimenopausal transition, against bioenergetic deficits and AD risks. Placebo or E2+CyP4 therapy was initiated on female rats at 9-10 months with either regular cycling or irregular cycling, and for each cycling status, ovariectomy (OVX) or Sham OVX surgery was performed before the intervention. Hormone therapy consisted of two 30-day cycles of continuous E2 and cyclic P4 (10 days/cycle) delivered by silastic capsules. Upon completion of the regime, rats were subject to genomic, biochemical and brain metabolic investigations. We previously reported that a two-month treatment of E2+CyP4 on (OVX) young rats induced a bioenergetic gene-expression profile comparable to the ovary intact females. Our data from this study suggest that E2+CyP4 therapy improves brain bioenergetic functions in terms of increased pyruvate dehydrogenase (PDH) activity and elevated mitochondrial respiratory capacity, but the effect was differentially affected by the endocrine status of the rats when the intervention was initiated. Interestingly, our data suggested that OVX initiated on regular or irregular cyclers elicited opposed effects on bioenergetic-, inflammatory- and AD-related gene expressions. Outcomes of this study determine the window of opportunity for preventing the at-AD-risk bioenergetic phenotype by hormone intervention and will provide mechanistic details for developing novel strategies to maintain neurological health and function throughout menopausal aging.

Disclosures: Z. Mao: None. **F. Yin:** None. **J. Yao:** None. **R. Brintion:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.18/CC18

Topic: C.01. Brain Wellness and Aging

Support: NIA P01 AG26572

NIH T32 AG052374-01

Title: Estradiol improves metabolic and cognitive outcomes of obesity in female APOE3 and APOE4 mice at early middle age

Authors: *A. CHRISTENSEN[1], C. J. PIKE[2]
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Abstract: Alzheimer's disease (AD) is a multifactorial neurodegenerative disease that is more prevalent in females. AD risk is significantly affected by genetic, environmental, and modifiable factors. The most significant genetic risk factor for AD is the ε4 allele of apolipoprotein E (*APOE4*). Interestingly, AD risk associated with *APOE4* disproportionately affects women. Further, human and rodent studies indicate that neuropathology and cognitive deficits associated with *APOE4* are greater in females. Modifiable lifestyle factors also affect AD risk. One such factor is obesity during middle-age, which significantly increases AD risk in late life. Given that ~65% of US adults are overweight or obese, it is important to understand not only how obesity independently affects AD risk but also (a) how it interacts with *APOE4* to affect AD and (b) the extent to which these interactions can be reduced by therapeutic strategies. A widely used intervention in middle-aged women is estrogen-based hormone therapy, which can exert wide-ranging health benefits when administered in early middle-age at perimenopause, but is potentially harmful in late middle-age. No experimental studies have explored the interactions among *APOE4*, obesity, and hormone therapy in aging females. To begin investigating these issues, we considered how obesity outcomes are affected by treatment with estradiol at the onset of middle-age in female mice with human *APOE3* and *APOE4*. The utilized transgenic mice (called EFAD non-carriers, EFAD-NC) have targeted replacement of mouse *APOE* with human *APOE3* or *APOE4* and are generated from breeding of EFAD-Tg mice, which are homozygous for human *APOE3* or *APOE4* against a hemizygous background of 5xFAD-Tg mice. Female EFAD-NC mice were examined over a four-month period that spans the transition into reproductive senescence, which models many aspects of human perimenopause. Beginning at age 5 months, mice were maintained on a control diet (10% fat) or nutrient-matched high-fat diet (60% fat). After 2 months of diet, by which time obesity was present in high-fat groups, all mice were implanted with either estradiol or vehicle that was maintained for the final two months of the experimental period. Animals were assessed on a wide range of metabolic and neural measures. In general, hormone therapy improved metabolic outcomes and cognitive performance in both *APOE3* and *APOE4* mice, although the efficacy sometimes differed across genotype and diet condition. Collectively, these findings begin to define how *APOE4* interacts with female sex, perimenopause and obesity to regulate neural outcomes and the extent to with hormone therapy provides benefits.

Disclosures: A. Christensen: None. **C.J. Pike:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.19/CC19

Topic: C.01. Brain Wellness and Aging

Support: NIH/NIA P01AG026572

Alzheimer's Association SAGA-17-419459

Title: Impact of APOE genotype on the sex-differentiated bioenergetic trajectories and AD risks in aging mouse brains

Authors: *F. YIN[1], Y. WANG[1], A. MISHRA[1], Z. MAO[1,2], R. D. BRINTON[2,1]
[1]Sch. of Pharm., USC, Los Angeles, CA; [2]Ctr. for Innovation in Brain Sci., Univ. of Arizona, Tucson, AZ

Abstract: Age, APOE4 genotype, and female sex are top risk factors for AD. Our previous studies demonstrated that the bioenergetic shifts occurring in the perimenopausal female brain could contribute to an increased AD risk in women. We also observed substantial sex disparities in brain bioenergetic trajectories in normal aging mice. The goal of this study is to determine the sex differences in the impact of APOE genotype on AD at-risk phenotypes during brain aging. Female and male, APOE3- and APOE4 targeted replacement (TR) mice were assessed for: (a) bioenergetic-, inflammatory-, and AD pathology-related gene expression in hippocampus followed by bioinformatic analysis, and (b) key metabolic parameters in the periphery. Gene expression analyses revealed that female APOE4 mice at pre-menopause age (6-month old) exhibited a significantly different bioenergetic profile relative to APOE3 controls: APOE4 mice showed a higher expression of genes involved in mitochondrial oxidative phosphorylation, mitochondrial membrane transport, and mitochondrial fusion. These changes in female APOE4 brains may represent an adaptive response to deficits in brain glucose availability and a shift in energy fuels from glucose to ketone bodies and glucose. This hypothesis is further supported by: (a) APOE4 mice had lower levels of plasma glucose in both sexes while the higher levels of ketone bodies and triglycerides were only seen in the females; (b) both APOE3 and APOE4 females had lower peripheral glucose levels and higher ketone body levels than their genotype-matched male counterparts, indicating a potential earlier shift in bioenergetic fuel usage in females. These findings suggest that APOE4 genotype interacts with the age-related decline in glucose metabolism and the bioenergetic shift to alternative fuels, particularly in females. Functional assessments of these mice including: (a) FDG-microPET for cerebral glucose metabolism, (b) brain mitochondrial function, and (c) glucose tolerance test for peripheral metabolism, are undergoing. Outcomes of this study will provide mechanistic details of the APOE4 genetic burden on the sex-differentiated bioenergetic fluctuation during aging and its contribution to higher AD risks in women. This work was supported by NIA P01AG026572 and Alzheimer's Association SAGA-17-419459 to RDB.

Disclosures: **F. Yin:** None. **Y. Wang:** None. **A. Mishra:** None. **Z. Mao:** None. **R.D. Brinton:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.20/CC20

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant P01AG026572 to RDB

Title: Epigenetic control of the perimenopausal brain in hypothalamus

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Abstract: To better understand the potential underlying mechanisms of neurological symptoms associated with perimenopause transition, as well as the temporal control of the onset and completion of perimenopause, the current study aims to characterize the transcriptional and epigenomic changes that occur during the transition using a rat model recapitulating fundamental characteristics of human perimenopause. RNA-seq analysis of hypothalamic tissues from rats at various ages and endocrine status showed that the majority of differentially expressed genes occurred between 6-9 months of age, prior to perimenopause, when animals were still regularly cycling. E2, GnRH, and KISS1 were identified as upstream regulators involved in the transition between each endocrine status suggesting that hypothalamic aging begins before the onset of perimenopause and progresses through the transition into menopause. One-carbon key players SAM and homocysteine were identified as regulators of transcriptional changes during 6-9 months, suggesting that impaired one carbon metabolism precedes irregular cycling. Pathway analysis of RNA-seq and reduced representation bisulfite sequencing (RRBS) genome wide DNA methylation data identified GnRH signaling and the hypothalamic-pituitary-gonadal axis (HPG axis), prolactin, glutamate and GABA signaling, melatonin and circadian rhythm, as well as epigenome maintenance and one-carbon metabolism, as pathways that undergo dramatic changes during perimenopause. Hypothalamic global DNA methylation declined at the onset of irregular cycling in 9 month animals, and two distinct populations of high and low methylation were observed at 6 months of age demonstrating differences in epigenome “age”. To determine if DNA methylation directly influences onset and progression of perimenopause, we treated pre-menopausal rats with 5-aza-2’-deoxycitidine (5-aza), a de-methylating agent, and assessed cyclicity and perimenopause timing. 5-aza treatment significantly accelerated the completion, but not initiation, of perimenopause, as characterized by acyclicity. Conversely, methionine supplementation delayed the initiation of perimenopause, and resulted in a larger proportion of animals still cycling regularly at 9 months of age. These data together provide evidence that endocrine aging in hypothalamus begins before the onset of the physical manifestation of

perimenopause (i.e. irregular cycling) and that epigenetics, including DNA methylation, regulate the onset and completion of the perimenopause transition.

Disclosures: E. Bacon: None. **A. Mishra:** None. **Y. Wang:** None. **F. Yin:** None. **R.D. Brinton:** None.

Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.21/CC21

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant AG033288

NIA Grant P01AG026572

Title: PhytoSERM for management of menopause-associated vasomotor symptoms -- effect of APOE genotype and mitochondrial haplogroup

Authors: *Y. WANG[1], G. HERNANDEZ[1], W. MACK[2], L. S. SCHNEIDER[2], F. YIN[1], R. D. BRINTON[1,3]
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Abstract: PhytoSERM is a selective estrogen receptor beta (ERβ) modulator comprised of three clinically relevant phytoestrogens: genistein, daidzein, and equol. Earlier *in vitro* and *in vivo* studies demonstrated neuroprotective effect of PhytoSERM, without side effect on the reproductive system. In a mouse model of hot flash, 8-week PhytoSERM diet prevented surgical menopausal-induced rise in tail temperature. In the present study evaluating safety and efficacy of PhytoSERM for menopause-associated hot flashes (ClinicalTrial.gov ID: NCT01723917), 44 post-menopausal women aged 48 to 58 years old with a vasomotor symptom such as hot flash and a memory complaint were included. Participants were randomized into placebo (N=16), 50mg (N=17), or 100mg (N=11) daily dosage groups. Frequency and severity of hot flash were self-reported throughout the 12-week trial period. Changes in hot flash frequency within each treatment group were analyzed using non-parametric paired t-test between week 1 and week 12, and changes among treatment groups were analyzed using non-parametric ANOVA followed by unpaired t-test. Results were then stratified based on the APOE genotype and mitochondrial haplogroup of the participants. At week 12, participants on both the 50mg and the 100mg PhytoSERM groups had significantly lower hot flash frequencies compared to week 1. However, only the 50mg group demonstrated significant reduction compared to the placebo group, supporting 50mg daily as a more effective dosage for management of hot flash. When stratified

by APOE genotype, non-APOEε4 carriers on 50mg group had significantly reduced hot flash frequencies compared to those from the placebo group. APOEε4 carriers on 50mg of PhytoSERM also had a trend of reduced hot flash frequency, but failed to reach statistical significance, likely due to limited sample size. When stratified by mitochondrial haplogroups, haplogroup H on 50mg of PhytoSERM had significantly reduced hot flash frequency compared to those on placebo, whereas non-H haplogroups had a trend of reduction but failed to reach statistical significance. Collectively, daily treatment of PhytoSERM at 50mg significantly reduced hot flash frequency in post-menopausal females, with non-APOEε4 carriers and haplogroup H more responsive to the treatment. A larger cohort is necessary to further identify and confirm responders based on APOE genotype and mitochondrial haplogroups. This work was supported by NIA R01AG033288 to LSS and P01AG026572 to RDB.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.22/CC22

Topic: C.01. Brain Wellness and Aging

Support: NIH/NIA P01AG026572

Title: Mechanistic role of brain hypometabolism and mitochondrial uncoupling in perimenopausal hot flash

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Abstract: The goal of the current study is to determine the mechanism of the signature symptom of the menopausal transition, the perimenopausal hot flash. We hypothesized that loss of ovarian hormone regulation of bioenergetics in brain induces a series of adaptive responses in the brain, which are initiated by decline in glucose metabolism, followed by activation of alternative fuel sources, ketone bodies and free fatty acids, which lead to mitochondrial uncoupling and temperature dysregulation. We used the ovariectomy (OVX) rat model as a reliable and predictive inducer of temperature dysregulation. Loss of ovarian hormones in the OVX rats led to decreased uterine weight, increased body weight and a significant increase in peripheral (tail skin) temperature. Further, our analyses in the OVX rat model indicated that peripheral temperature dysregulation coincided with systemic glucose intolerance and decreased cerebral glucose metabolism (FDG-PET). We further tested our hypothesis that loss of ovarian hormones

leads to disruption and uncoupling of the proton motive force-dependent energy conservation systems and the consequent dissipation of energy as heat. Results of these analyses indicated that mitochondrial respiratory control ratio (RCR) was decreased in OVX rats accompanied by increased mitochondrial uncoupling, the upregulation of mitochondrial uncoupling proteins (UCPs), and enhancement of mitochondrial fragmentation in multiple brain regions. These OVX-induced changes were completely or partially prevented by 17beta-estradiol treatment, suggesting an obligatory role of estrogen signaling in these events. Finally, to investigate the relationship between mitochondrial uncoupling in the brain and the increase in peripheral temperature, mitochondrial uncoupling was induced by 2,4-dinitrophenol (2-DNP), a mitochondrial uncoupler. Our analyses indicate that intracerebroventricular injection of 2-DNP induced sequential fluctuations in brain temperature, core temperature and tail skin temperature, with the endogenous mitochondrial uncouplers (UCP2 and UCP3) downregulated in the brain, likely a negative feedback to the 2-DNP-induced mitochondrial uncoupling. Collectively, we established the physiological and bioenergetic phenotype of a rat model of hot flash, and our findings provide new mechanistic details of hot flash by connecting loss of ovarian hormones, brain hypometabolism, mitochondrial uncoupling and dysfunction, and peripheral temperature dysregulation. This work was supported by NIA 5P01AG026572 to RDB; Project 5 to RDB.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

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Alzheimers association SAGA-17-419459

Paul Slavic Trust

Title: Sex differences in metabolic and neurological outcomes in humanized APOE-E4 knock-in rats

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Abstract: Women APOE-ε4 carriers are at increased risk of developing Alzheimer's disease (AD) than men, and are susceptible to accelerated aging and undergo faster rates of cognitive

decline from Mild Cognitive Impairment (MCI) to AD. Using a novel rat model with humanized APOE-**ε**4 gene knock-in (Horizon Discovery), we conducted a 9-month longitudinal study (between age 6-15 months) to characterize the individual and combinational impact of sex and APOE-ε4 genotype on the brain aging process by evaluating metabolic and neurological outcomes. APOE-ε4 and wildtype (WT), male and female rats, were metabolically assessed at four aging windows during the study: 7-8 months (m), 9-10 m, 12-13 m and 15-16 m. Vaginal lavages were collected from APOE-ε4 and WT rats during the following aging windows 6-7 m, 9-10 m and 12-13 m to correlate reproductive aging with corresponding changes in metabolic and neurological outcomes. Across these aging windows**,** we conducted micro ^{18}FDG-microPET/CT (18-fludeoxyglucose micro Positron Emission Tomography / Computational Tomography) to measure brain glucose uptake, and established peripheral metabolic- and inflammatory profile consisting of ketone bodies, triglycerides, insulin, lipidomics as well as circulating cytokines: IFN-γ, IL-1β, IL-4, IL-5, IL-6, IL-10, IL-13, TNF-α. Longitudinal follow-up revealed that in comparison to WT rats, APOE-ε4 rats had significantly elevated plasma triglyceride levels across all aging windows, in both sexes. Male APOE-ε4 rats had the highest triglyceride, ketone body and insulin levels across all groups at all ages. In APOE-ε4 females, age related decline in insulin levels while increase in ketone body levels was evident. Brain glucose uptake, as determined by FDG-PET, was significantly higher in APOE-ε4 males than APOE-ε4 females at 9-10 m and 12-13 m. APOE-ε4 females experienced a significant decline in glucose uptake when undergoing the perimenopausal transition indicative of a state of bioenergetic deficit after the perimenopausal transition. While during the same aging transition, male APOE-ε4 rats did not show any significant changes in brain glucose uptake. Therefore, the decline of glucose uptake coincident with increase in ketone body levels in females may reflect a metabolic shift from relying solely on glucose towards that utilizing both glucose and ketone bodies, which may be correlative to the increased white matter catabolism as we reported previously. Collectively, this longitudinal study will facilitate the identification of optimal intervention windows in APOE-ε4 carriers and peripheral metabolic markers predictive of neurological changes.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 678.24/CC24

Topic: I.02. Systems Biology and Bioinformatics

Support: NSERC-CREATE

CIHR

Title: Expression analysis of mouse models and patients of neurodegenerative diseases

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Abstract: Neurodegenerative diseases (NDs) - including Alzheimer's disease (AD), Parkinson's disease (PD), and spinocerebellar ataxias (SCA) - all share the common feature of intra- and extracellular protein deposits. Most NDs are sporadic, and are not inherited in a monogenic Mendelian way; only 5-10% of PD and less than 10% of AD cases are thought to have a genetic component. Still, animal models based on familial mutations are used to study idiopathic forms of NDs, as both forms are believed to be consequence of similar pathogeneses. A shared mechanism of disease in idiopathic and familial NDs is supported by almost identical clinical and pathological findings in the two forms. The field has devoted substantial resources to the study of idiopathic NDs: through the use of next generation sequencing, genome wide genetic screens in humans and in animal models of disease, and finally by attempting to identify traits of disease risk by comparing patients with controls. However, a combined quantification of the results of the different datasets has yet to be done. Here we propose an approach to combine these datasets. We use meta-analytical statistical methods to find genes showing patterns of consistent differential expression in human and mouse PD and SCA3.

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Poster

678. Tauopathies, Tau-Dementias, and Prion Diseases I

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Title: Small ubiquitin-like modifier (SUMO) impacts on neuronal function and neurodegeneration

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Abstract: SUMOylation plays important roles in cellular events and is involved in several aspects of neuronal development and function. SUMO exists as three isoforms, SUMO1 and SUMO2/3, which display approximately 50% sequence homology. It has been reported that SUMO1 and SUMO2/3 function to regulate proteins in several ways including subcellular localization, nuclear transport, transcriptional repression, and cell cycle progression. To investigate the functional consequences of SUMOylation, we generated a SUMO1 transgenic model and identified ~100 candidate SUMO1 conjugated proteins by proteomic analysis. A number of cytoskeletal proteins, including the microtubule associate tau protein, were found to be SUMOylation targets that are involved in the development and maintenance of dendritic spines. To examine the links between tua and SUMOylation in more detail, we focused on the relationship between SUMO1 and tauopathies which are a class of neurodegenerative diseases characterized by the accumulation of abnormal hyperphosphorylated tau as neurofibrillary tangles (NFTs). Tauopathies encompass a broad range of disorders including Alzheimer's and Pick's disease, Frontotemporal Dementia with Parkinsonism (FTDP-17), corticobasal degeneration (CBD), chronic traumatic encephalopathy (CTE) and progressive supranuclear palsy (PSP). We examined the impact of SUMOylation on tau and found that the conjugation of SUMO1 modulates tau misfolding and accumulation both in vitro and in vivo. SUMO isoform-specific effect of tau aggregation was observed that was also dependent on the particular tau isoforms. These results suggest a significant contribution of SUMO1 modification to neuronal function and also have implications for the mechanisms of neurodegeneration involving tau pathology.

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Poster

679. Somatosensation: Spinal Circuits

Location: Halls A-C

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Program#/Poster#: 679.01/CC26

Topic: B.04. Ion Channels

Support: R01NS087033

R01NS087033-02S1

Title: Role of calcium release activated calcium (CRAC) channels in P2X7R-mediated cytokine production

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Abstract: Spinal astrocytes respond to peripheral inflammation by releasing cytokines, which are thought to be involved in central mechanisms underlying the maintenance and exaggeration of chronic pain. The specific molecular mechanisms that control cytokine production from reactive astrocytes remain largely unknown. Ca^{2+} signals in astrocytes mediate a remarkable variety of cellular functions, including glutamate release and cytokine production. Among the various mechanisms by which cellular Ca^{2+} signals are generated, store-operated calcium channels (SOCs) have recently emerged as a widespread pathway for regulating many Ca^{2+}-dependent functions. ATP can activate a wide variety of pathways through P2 purinoreceptors, allowing downstream effects that can lead to neuroprotection and pathology in the CNS. The P2X7 receptor (P2X7R) is a well-defined ionotropic cation channel that plays a key role in the development of chronic pain associated with nerve injury and inflammation. Recently, we have demonstrated that SOC proteins are expressed and functional in astrocytes. SOC activation increased TNF-α and IL-6 production in cultured astrocytes. Here we report that SOC activation with thapsigargin (TG) and P2X7R activation with ATP and the specific P2X7R agonist 2′(3′)-O-(4-Benzoylbenzoyl) adenosine 5′-triphosphate (BzATP) increases phosphorylation of ERK and CaMKII and subsequently stimulates production of IL-6 in cultured astrocytes. Interestingly, ATP- and BzATP-induced cytokine production was attenuated by SOC inhibitors YM58483 and 2-APB, and knockdown of SOC pore-forming subunits known as CRAC channels (Orai1, 2, 3) attenuated IL-6 production in a store-independent manner. These findings implicate a link between SOCs and P2X7R in astrocyte-mediated cytokine release.

Disclosures: F.M. Munoz: None. **X. Gao:** None. **J. Xia:** None. **J. Jiang:** None. **H. Hu:** None.

Poster

679. Somatosensation: Spinal Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 679.02/CC27

Topic: B.04. Ion Channels

Support: R01NS087033

R21NS077330

Title: STIM1 plays a role in spinal cord synaptic transmission

Authors: *J. XIA[1], F. M. MUNOZ[2], R. JEAN-TOUSSAINT[3], H. HU[2]
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Abstract: Increasing evidence indicates store-operated calcium channels (SOCs) in the nervous system contribute to neuronal Ca^{2+} signaling. STIM1, an ER Ca^{2+} sensor, plays a critical role in the activation of Orai channels that mediate store-operated Ca^{2+} entry (SOCE). Our recent studies suggest that SOCs are expressed and functional in spinal cord dorsal horn neurons and are involved in central sensitization. Its underlying mechanisms remain elusive. Here we found that STIM1 is mainly expressed in projection neurons and excitatory interneurons, but not in GABAergic neurons in the spinal cord dorsal horn. To determine whether STIM1 plays a role in spinal cord long term potentiation (LTP), we made conditional knockout (KO) mice in which STIM1 is deleted in vesicle glutamate transporter (VGLUT2) positive neurons and recorded field excitatory postsynaptic potentials (fEPSPs) evoked by dorsal root stimulation in the superficial dorsal horn. LTP was induced by high-frequency stimulation (HFS) of a dorsal root, which lasted for at least one hour in the spinal cord from wild type mice. However, the induction of LTP was dramatically attenuated in the spinal cord from STIM1 KO mice, suggesting STIM1 plays a role in synaptic plasticity. Furthermore, we found that AMPA-induced Ca^{2+} influx was reduced in STIM1 KO spinal cord dorsal horn neurons, but GluA1 and GluA3 protein levels were not altered in KO mice, indicating a regulatory role of STIM1 in AMPAR-mediated Ca^{2+} signaling in the spinal cord dorsal horn. Together, the results in the present study demonstrate that STIM1 plays a role in the development of spinal LTP presumably due, in part, to the regulation of AMPAR. These findings indicate an important role of STIM1 in spinal cord synaptic transmission that contributes to central sensitization.

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Poster

679. Somatosensation: Spinal Circuits

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Topic: D.02. Somatosensation

Support: NHMRC grant 63100

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Title: Heteromeric glycine receptors regulate the excitability of inhibitory interneurons via phasic and tonic inhibition

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Abstract: The spinal cord dorsal horn contains inhibitory interneurons (INs) that release GABA and glycine. Both neurotransmitters can activate synaptic and extrasynaptic receptors to mediate phasic and tonic inhibition, respectively. In the dorsal horn and brain, GABA receptors with different subunit composition can be targeted to synaptic and/or extra-synaptic locations. Here we ask whether glycine receptors with different subunit composition can also be directed to synaptic and extrasynaptic sites in parvalbumin (PV) expressing inhibitory INs. Adult mice (P60-90, both sexes) were deeply anaesthetized with ketamine (100 mg/kg, i.p.) and decapitated. Transverse spinal cord slices (300 um thick) were prepared from the lumbar cord and whole cell recordings were obtained using a CsCl-based internal. Phasic glycinergic inhibition dominated in PVINs, because mIPSCs were bicuculline (10 uM) and picrotoxin (50 uM) resistant, and completely abolished by strychnine (1 uM). Peak scaled non-stationary noise analysis on these mIPSCs estimated mean single channel conductance at 36 ± 3 pS (n = 20). This is consistent with synaptic clustering of heteromeric beta-subunit containing glycine receptors. We also showed that PNINs are under tonic glycinergic inhibition (n=14) because holding current and baseline noise were not affected by bicuculline and picrotoxin, whereas strychnine reduced mean amplitude and baseline noise by ~100 pA and ~10 fold, respectively. Conversely, addition of glycine transporter blockers increased holding current and baseline noise. Non-stationary noise analysis, undertaken on the tonic current during the onset of strychnine block, estimated mean single-channel conductance to be 29 ± 1 pS (n = 19). These data are consistent with the tonic current being mediated by heteromeric beta subunit-containing glycine receptors. Enhancing tonic inhibition with glycine transporter blockers reduced action potential (AP) discharge frequency in PVINs (n = 23), whereas addition of strychnine had the opposite effect (n = 14). To assess whether endogenous glycine, released by synaptic activity, could also influence PVIN excitability we evoked glycine-mediated currents using an extracellular bipolar stimulating electrode. Evoked glycine currents increased holding current and baseline noise by 82 ± 46 pA and 200%, respectively (n = 10) and modulated AP discharge in a third of neurons tested. Together, these data suggest: 1) glycine subunit composition is similar at synaptic vs. extrasynaptic sites on PVINs; and 2) tonic glycine-mediated inhibition can modify the output of PVINs and alter how spinal circuits process sensory information.

Disclosures: M.A. Gradwell: None. **D.I. Hughes:** None. **R.J. Callister:** None. **B.A. Graham:** None.

Poster

679. Somatosensation: Spinal Circuits

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Topic: D.02. Somatosensation

Support: NS072202

Title: Regulation of spinal nociceptive processing by the Na^+ leak channel NALCN

Authors: *N. C. FORD[1], D. REN[2], M. L. BACCEI[1]
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Abstract: Recent work suggests that a tonic conductance mediated by the Na^+ leak channel NALCN increases the intrinsic membrane excitability of spinal lamina I projection neurons (PNs) and can be enhanced by substance P (SP) signaling. However, the degree to which NALCN is required for SP-evoked activation of spinal PNs, and its potential role in regulating pain sensitivity, remains unclear. To address this issue, NALCN was deleted in spino-parabrachial (PB) neurons via the injection of AAV1-hSyn-Cre-eGFP into the lateral parabrachial nucleus of C57BL6 $NALCN^{fl/fl}$ mice on postnatal day (P) 3. Similar injections of AAV1-hSyn-GFP were used as a control. Whole-cell patch clamp recordings were obtained from GFP-labeled spino-PB neurons using in vitro spinal cord slice preparations on P10-14. Bath application of 5 µM SP evoked significantly weaker membrane depolarization and fewer action potentials in NALCN-knockout PNs compared to PNs infected with AAV1-hSyn-GFP, suggesting that the SP-dependent output of spinal pain circuits is shaped by NALCN activity. To characterize the functional implications of NALCN expression within the spino-PB pathway for pain sensitivity, ongoing studies are comparing mechanical and thermal withdrawal thresholds in mice injected with AAV1-hSyn-Cre-eGFP or AAV1-hSyn-GFP into the PB. Spontaneous pain behaviors in response to the intraplantar injection of capsaicin will also be examined following the deletion of NALCN within spino-PB circuits. The current results suggest that NALCN channels are critical mediators of SP-induced excitation of ascending projection neurons during early life. This raises the possibility that the level of NALCN conductance in this population influences pain perception in the developing brain.

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Poster

679. Somatosensation: Spinal Circuits

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Topic: D.02. Somatosensation

Support: BBSRC Grant BB/N006119/1

Title: The role of neuropetide-Y expressing dorsal horn inhibitory interneurons in nociceptive and pruriceptive circuits

Authors: *K. A. BOYLE, E. POLGAR, A. C. DICKIE, A. J. TODD
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Abstract: Previous work from our laboratory has identified neuropeptide Y (NPY)-expressing neurons of the dorsal horn as a subpopulation of inhibitory interneurons that are well placed to modulate spinal nociceptive circuits through connections with nociceptive projection neurons and other dorsal horn interneurons (Iwagaki et al. (2016), Pain 157:598-612). A recent study that aimed to ablate or silence dorsal horn NPY-expressing interneurons (NPY-INs) in the RH26 *NPY::Cre* mouse line reported no effects on acute mechanical or thermal nociception (Bourane et al. (2015), Science 350:550-554). However, the method employed in that study will also have captured a broader population of inhibitory interneurons that transiently express NPY. Here we demonstrate that intraspinal injection into adult RH26 mice of adeno-associated viruses (AAVs) carrying Cre-dependent constructs allows for much more specific targeting of NPY-INs. We have used this method to achieve reliable and relatively specific activation of NPY-INs through injection of an AAV construct that expresses the excitatory DREADD hM3Dq (together with the fluorescent protein mCherry) in a Cre-dependent manner. We then assessed the effects of NPY-IN activation on nociceptive circuit activity and behaviour. Following systemic administration of the hM3Dq agonist clozapine N-oxide (CNO), we were able to detect the transcription factor Fos (a marker of neuronal activation) in the vast majority of virally-infected Cre-expressing neurons in laminae I-III. However the proportion of mCherry-negative neurons in laminae I-II that expressed Fos following a noxious heat stimulus was significantly lower in CNO-treated animals compared to vehicle-treated controls, suggesting NPY-IN activation can inhibit neurons that are normally activated by noxious thermal stimuli. In agreement with this conclusion, CNO-treated mice displayed a significantly longer latency of withdrawal from a radiant heat source (Hargreaves test) compared to vehicle-treated controls, although this effect was mild. A much more robust increase in mechanical withdrawal threshold was also observed in CNO-treated mice. DREADD-mediated activation of NPY-INs also markedly reduced itch-related behaviour in mice that received an intradermal injection of the pruritic agent chloroquine. Our results

highlight NPY-INs as an important inhibitory element in dorsal horn circuits that process acute pain- and itch-related signals.

Disclosures: **K.A. Boyle:** None. **E. Polgar:** None. **A.C. Dickie:** None. **A.J. Todd:** None.

Poster

679. Somatosensation: Spinal Circuits

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Topic: D.02. Somatosensation

Support: SNF 310030_15639/1

Title: Gastrin releasing peptide boosts the functional output from spinal itch-processing circuits

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Abstract: Gastrin-releasing peptide (GRP) and its cognate receptor (GRPR) have been identified as important components in spinal cord pruriceptive-processing. However, the functional aspects of spinal itch-processing circuits are not well understood. Here, we combined electrophysiological and optogenetic approaches to functionally characterize GRP- and GRPR-positive neurons and to study their synaptic connectivity as well as modulation by GRP. We performed whole-cell patch-clamp recordings from GRP and GRPR neurons in acute spinal cord slices to characterize their intrinsic biophysical properties and firing patterns. We found that GRP neurons constitute a rather homogenous population with 92% of cells showing initial bursting firing. GRPR neurons were more heterogeneous comprising delayed (64%) and non-delayed (36%) firing subpopulations. We also found that delayed-firing GRPR neurons had significantly hyperpolarized resting membrane potentials (RMP), lower input resistances (Ri) and higher rheobase compared to GRP neurons. These characteristics are consistent with delayed-firing GRPR cells being glutamatergic neurons involved in integrating and transmitting the spinal itch information. We then characterized the synaptic connectivity between GRP- and GRPR-positive neurons in slices prepared from GRP-ChR2_GRPR::eGFP mice and found that GRP neurons were synaptically connected to GRPR neurons. Under baseline conditions, light stimulation of ChR2-expressing GRP cells induced sub-threshold responses in GRPR neurons. Application of 300 nM GRP caused a slow depolarization of delayed-firing GRPR neurons, which often resulted in ongoing action potential firing after several minutes. Moreover, in the presence of exogenous GRP, the same light stimulation paradigm triggered action potential firing in GRPR delayed neurons. Our results represent a detailed physiological characterization of

GRP- and GRPR-cells involved in spinal pruriceptive processing and suggest that GRP acts as an essential positive modulator to enhance the output of itch-processing circuits.

Disclosures: **M. Pagani:** None. **H. Johannssen:** None. **H.U. Zeilhofer:** None.

Poster

679. Somatosensation: Spinal Circuits

Location: Halls A-C

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Program#/Poster#: 679.07/CC32

Topic: D.02. Somatosensation

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Title: Gastrin releasing peptide neurons in itch processing circuits of the spinal cord

Authors: *G. W. ALBISETTI[1], L. HÖSLI[1], H. WILDNER[1], H. U. ZEILHOFER[1,2]
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Abstract: Itch, also known as pruritus, is an irritating cutaneous sensation that induces a scratch reflex. Itch has evolved to detect the presence and consequently to promote the removal of harmful agents. However, in several cutaneous and systemic diseases, itch can also become chronic, thus severely affecting the quality of life. Yet, the mechanisms that drive itch sensations are not fully understood. Previous studies have shown that spinal neurons that express gastrin-releasing peptide receptor (GRPR) are required specifically for chemically induced pruritic behaviors. Our study aims to better understand the neural circuit that provides input to GRPR neurons. To this end, we have characterized and manipulated neurons in which Cre is expressed under the control of the GRP gene, the gene that codes for the GRPR ligand. Immunohistochemical studies identified the GRP+ cells as a subset of excitatory interneurons, which are present in laminae I and II of the spinal dorsal horn. Moreover, GRP+ cells were found to receive direct synaptic contacts from MrgprA3+ neurons (a subset of primary afferent fibers associated with itch). Behavioral analysis of mice after ablating GRP+ neurons showed specifically reduced itch responses to chloroquine, histamine and serotonin. Conversely, activation of GRP+ cells showed and increased spontaneous and pruritogen-induced scratching behavior. Responses to painful thermal and mechanical stimuli were unaffected by the loss or activation of GRP+ neurons. Taken together, our results indicate a specific role of GRP+ neurons in spinal itch processing circuits.

Disclosures: **G.W. Albisetti:** None. **L. Hösli:** None. **H. Wildner:** None. **H.U. Zeilhofer:** None.

Poster

679. Somatosensation: Spinal Circuits

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Support: Wellcome Trust (grant 102645)

BBSRC (grant BB/N006119/1)

Title: A comparison of morphology and function of gastrin-releasing peptide and substance-P expressing interneurons in the spinal dorsal horn

Authors: *A. BELL[1], A. DICKIE[1], N. IWAGAKI[1], R. KELLY[1], S. WEST[2], M. GUTIERREX-MECINAS[1], E. POLGAR[1], A. J. TODD[1]
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Abstract: Numerous interneurons are present in the superficial dorsal horn of the spinal cord and these cells regulate the transmission of information perceived as touch, pain, or itch. Despite the importance of these cells, our understanding of their roles in the neuronal circuitry is limited by the difficulty in identifying functional populations. We have previously identified two non-overlapping groups of excitatory interneurons in the mouse dorsal horn defined by the expression of either gastrin-releasing peptide (GRP) or substance P. Here we aim to provide evidence that differences exist in the morphology of these cells, their synaptic inputs and their response to nociceptive and pruritic stimuli which suggest they represent two functional populations.
To allow comparison of dendritic morphology, individual cells were digitally reconstructed. Reconstructions of GRP-expressing cells were based on confocal scans of Neurobiotin filled cells from a transgenic GRP-EGFP mouse. Substance P-expressing dendritic arbours were traced from single cells revealed by Cre-dependent Brainbow viral injection in $Tac1^{Cre}$ mice. Substance P-expressing cells appear to be of predominantly radial morphology, while GRP cells are either unclassified or central. Detailed morphometric parameters were extracted from reconstructions enabling hierarchical cluster analysis. Based on this, the two cell populations can be divided into two well defined clusters demonstrating they are morphologically distinct.
GRP cells do not respond to pruritic stimulation by expressing fos or phosphorylating ERK. This is in contrast to substance P-expressing cells many of which respond to noxious thermal and mechanical stimuli and to intradermal injection of pruritogens. Further to this we show that ERK phosphorylation also seldom occurred in GRP cells following pinch, capsaicin or heat stimulation. To determine if different patterns of input underlie this differential responsiveness, we have determined the synaptic inputs to these cells via an immunofluorescence approach using the post-synaptic marker Homer. Substance P-expressing cells appear to receive a greater proportion of synapses from other excitatory interneurons than the GRP cells. GRP cells also

receive synapses from VGLUT3 expressing C-LTMR primary afferents which may have implications for their function.
Despite distinct differences between these two cell populations, their exact functional roles remain unclear. Substance P-expressing excitatory neurons are likely to be important in the transmission of pain and itch, while the situation surrounding GRP expressing cells is more uncertain.

Disclosures: **A. Bell:** None. **A. Dickie:** None. **N. Iwagaki:** None. **R. Kelly:** None. **S. West:** None. **M. Gutierrex-Mecinas:** None. **E. Polgar:** None. **A.J. Todd:** None.

Poster

679. Somatosensation: Spinal Circuits

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Topic: D.02. Somatosensation

Title: Expression of metabotropic glutamate receptors in the rat spinal cord

Authors: *M. OKUBO, H. YAMANAKA, K. KOBAYASHI, K. NOGUCHI
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Abstract: Glutamate is released as a neurotransmitter by most excitatory synapses in the nervous system. It also plays a key role in the physiological excitatory circuit in the spinal cord and is involved in pathological neurotransmissions such as inflammatory and neuropathic pain conditions. The actions of glutamate are mediated by different types of receptors that are ionotropic (iGluRs, AMPA, NMDA and kainate) and metabotropic (mGluRs) ones. Although it is well-studied expression of iGluRs, that of mGluRs is not fully elucidated in the spinal cord. In this study, we examined expression of mGluRs (mGluR1-8) in the spinal cord in rats by using conventional RT-PCR and *in situ* hybridization histochemistry (ISHH). RT-PCR revealed that mGluRs mRNA, excepted for mGluR2 and 6, was detected in the spinal cord. We next examined expression pattern of mGluRs mRNA by ISHH. It showed that mGluR1 and 4 mRNAs were weakly expressed throughout the gray matter of the spinal cord. mGluR3 mRNA was expressed throughout the spinal cord and may be expressed not only in the neurons but also in the glial cells. mGluR5 and 7 mRNAs were expressed in the gray matter and were unevenly distributed to dorsal horn of the spinal cord, especially Lamina I-III. mGluR8 mRNA was relatively expressed in the gray matter of the spinal cord. mGluR2 and 6 mRNAs could not be detected in the spinal cord. These finding suggest that mGluR5 and 7, which were especially expressed in Lamina I-III of the dorsal horn, may have principal roles in the glutamate transmission that modulates pain signaling in spinal cord.

Disclosures: **M. Okubo:** None. **H. Yamanaka:** None. **K. Kobayashi:** None. **K. Noguchi:** None.

Poster

679. Somatosensation: Spinal Circuits

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Topic: D.02. Somatosensation

Support: NIH Grant NS080889

Title: Altered synaptic properties of the spinal, metabotropic GABAb receptor in female mice after neonatal injury

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Abstract: Early-life injury produces permanent changes in pain-transmitting neurocircuitry. However, the underlying mechanisms of how nociceptive circuits respond to and are affected by noxious stimuli remains to be elucidated. In the adult mouse spinal dorsal horn it has been shown that a reduction in fast inhibitory synaptic transmission through GABAa and glycine receptors results from neonatal hindpaw incision. However, there is a gap in knowledge regarding the effects of neonatal hindpaw incision on slow inhibitory synaptic transmission through metabotropic receptors like GABAb. The GABAb receptor is highly expressed in the superficial dorsal horn (SDH) of the spinal cord and has multi-faceted inhibitory actions at the neuronal synapse. In the presence of GABA, the receptor presynaptically inhibits calcium channels, thus reducing or preventing the release of neurotransmitter vesicles from the presynaptic cell. GABAb also activates potassium channels postsynaptically, and this causes an outward current that hyperpolarizes and prevents the cell from firing action potentials. This study focuses on two cell types in the SDH, inhibitory GABAergic interneurons that locally modulate pain circuits, and lamina I projection neurons which serve as the conduit for pain transmission from the spinal cord to the brain. Using *in vitro* patch-clamp electrophysiology in adult mouse spinal cord slices, this study has shown a larger postsynaptic outward current amplitude, evoked by the GABAb agonist baclofen, in projection neurons after neonatal hindpaw incision. Interestingly, the incision also caused a significant decay effect in the outward current, which is suggestive of increased GABAb receptor desensitization. This effect may play a role in the disinhibition involved in nociceptive processing. Incision had no effect on baclofen-induced outward current in mature GABAergic interneurons, indicating a cell type specific effect. In addition, incision did not alter the presynaptic actions of GABAb in either projection neurons or GABAergic interneurons. These results suggest that tissue damage during early life persistently alters

postsynaptic GABAb-mediated inhibitory signaling within spinal pain networks, specifically in SDH projection neurons.

Disclosures: C.L. Brewer: None. **M.L. Baccei:** None.

Poster

679. Somatosensation: Spinal Circuits

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Topic: D.02. Somatosensation

Support: Wellcome Trust 102645

Title: Differences between two well neurochemically defined excitatory interneuron populations in the mouse superficial dorsal horn

Authors: *M. GUTIÉRREZ MECINAS[1], A. DICKIE[1], N. IWAGAKI[1], M. HERAU[2], A. BELL[1], E. POLGAR[1], A. TODD[1]
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Abstract: The dorsal horn of the spinal cord is important because contains the first synapse of pain and itch pathways, and is a site at which significant modulation of nociceptive and pruritoceptive transmission can occur. Interneurons, which account for the great majority of neurons in laminae I-III, are diverse in terms of their structure and function and are complexly organized. They can be divided into two main groups: inhibitory (GABAergic and/or glycinergic) and excitatory (glutamatergic) neurons. Our group has described four largely non-overlapping populations among the inhibitory interneurons have been defined in laminae I-II based on expression of neuropeptide Y, parvalbumin, nNOS or galanin/dynorphin. More recently, we have also described another four neurochemically different groups among the excitatory interneurons: those with the expression of neurotensin, neurokinin B, gastrin-releasing peptide (GRP) or substance P.
Due to their anatomical location, neurons expressing either GRP or substance P are a very interesting group to be studied further. As shown in another poster (Bell et al) these two groups are morphologically different, but differences extend beyond that. Physiologically, they show predominantly different firing patterns, which scarcely overlap. Substance P expressing cells show mainly delayed or gap firing, while the GRP show transient firing or single spikes, which is particularly interesting as these patterns are not commonly associated with excitatory interneurons. GRP expressing cells respond to MOR agonists but not 5-HT and rarely receive input from TRPV1/M8 expressing primary afferents based on electrophysiological recordings. When long propriospinal projections of these cells axons are studied using spinal injection of neuron tracer it is interesting to see that substance P expressing cells send their axons several

segments cranially while the GRP cells remains close to the cell body.
These results strongly suggest that the GRP and the substance P excitatory interneuron populations might have completely different roles in processing somatosensory information.

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Poster

679. Somatosensation: Spinal Circuits

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Support: CIHR grant 14697

NIH grant R01NS047567

Title: Presynaptic facilitation of the monosynaptic reflex in humans and rats

Authors: Y. LI, A. M. LUCAS-OSMA, S. BLACK, K. K. FENRICH, M. J. STEPHENS, L. SANELLI, S. LIN, K. FOUAD, M. A. GORASSINI, *D. J. BENNETT
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Abstract: The monosynaptic stretch reflex is well known to be inhibited by presynaptic GABA receptors that shunt action potentials in the sensory Ia afferent terminals on motoneurons[1], reducing local transmitter release. However, less well appreciated are the seminal works of Barron and Matthews[2] and Wall[3] that show that the action potential (AP) often fails to propagate over the entire sensory afferent terminal field (leaving silent branches), likely because of branch point failure in these highly branched and long afferents. While this branch point failure is modulated with anesthesia and injury, we have a lack of understanding of its causes. Here we explore the simple hypothesis that GABA induced primary afferent depolarization (PAD) brings the AP closer to threshold and prevents branch point failure, thus *facilitating* afferent transmission and the monosynaptic reflex, especially heteronymous reflexes where there are long afferents involved with branch points far from their motoneuron terminals. We therefore examined heteronymous and homonymous (H-reflex) monosynaptic reflexes in humans and the influence of sensory and cortical inputs known to produce PAD. In some subjects tibialis anterior (TA) muscle tendon vibration (conditioning stimulation) inhibited the homonymous soleus monosynaptic reflex when applied at a 20 - 100 ms interval prior to the reflex, consistent with the action of classic GABA-mediated PAD and presynaptic inhibition[4]. However, the same conditioning stimulation (vibration) facilitated the H-reflex in other subjects, and in all subjects more diffuse conditioning stimuli (from TA or quadriceps nerves, or motor cortex) facilitated the

H-reflex. Furthermore, the heteronymous monosynaptic reflex from the quadriceps to the soleus was consistently facilitated by diffuse sensory or cortical stimulation, over a time course consistent with PAD. Using intracellular recording from rat motoneurons we found the same facilitation of heteronymous monosynaptic reflexes during PAD evoked by heteronymous sensory afferents. Then, using neurobiotin reconstructions and intracellular recordings from afferents, we found that GABA receptors on Ia afferents facilitate AP conduction by depolarizing the afferent sufficiently to prevent AP failure. In summary, in addition to its putative role in inhibitory shunting, GABA helps prevent AP failure in afferents and thus can also produce presynaptic facilitation of reflex transmission.
References: 1. Cattaert, D. & El Manira, A. *J Neurosci* **19** 1999. 2. Barron, D.H. & Matthews, B.H. *J Physiol* **85** 1935. 3. Wall, P.D. & McMahon, S.B. *Philos Trans R Soc Lond* **343** 1994. 4. Hultborn, H. et al., E. *J Physiol* **389** 1987.

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Poster

679. Somatosensation: Spinal Circuits

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Topic: D.02. Somatosensation

Support: Malaysian Ministry of Higher Education

BBSRC 172232-01

Title: Identification of spinal cord neurons that presynaptically inhibit c-nociceptors

Authors: *M. MUSTAPA, A. C. DICKIE, N. IWAGAKI, A. J. TODD, D. I. HUGHES
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Abstract: GABAergic interneurons account for 24-31% of cells in laminae I and II. Non-peptidergic C nociceptors central axons terminate in lamina II as a complex form known as type I synaptic glomeruli. These complex consist of GABAergic axons and dendrites, possibly arises from local inhibitory interneurons which mediated presynaptic inhibition. Calretinin (CR) is a marker that has been widely used to define excitatory interneurons in the SDH and it is also express in some inhibitory interneurons. Later studies using CR::eGFP mice showed ~10% of CR neurons populations in lamina II of the dorsal horn are inhibitory interneurons. These cells showed tonic firing and they are islet cells. Preliminary data suggests that these CR islet cells form axoaxonic synapses on C^{MrgD} nociceptors. The aim of this study was to further characterise

the anatomical and electrophysiological properties of CR islet cells, with a view to assessing their role in providing presynaptic inhibition to C fibers. We used multiple mouse lines for anatomical part of the study. First two were Nociceptin::eGFP and RORb::eGFP mice. Both of these eGFP cells labels inhibitory interneurons throughout the dorsal horn. We also used sparsely labelled $RorB^{CreERT2}$;Ai9 mice to look at the CR islet cells contact with IB4 labelled primary nociceptors and to look at the morphology. For the combined electrophysiological and morphological study, CR^{cre};Ai9 mice (in which CR cells express tdTomato) were crossed with Noc::eGFP mice, which resulted in double labelling of cells expressing both nociceptin and CR with eGFP and tdTomato. We found, CR-Noc::eGFP cells are present in 6.8% of all neurons in lamina II and 1.5-2.5% of those in laminae I and III. These cells are expressed by 25% of inhibitory interneurons in lamina II and 5-11% of those in lamina I and III. None of the four inhibitory neurochemical markers (NPY, nNOS, Galanin and Parvalbumin) are labelled with CR-Noc::eGFP neurons and ~30-40% of those expressed sst_{2A} receptor. We found 28% of sparselly labelled $Rorb^{CreERT2}$ Ai9 mice boutons contacted IB4 terminals and appear to be islet morphology. Half of excitatory synapses on Rorb cells come from IB4 boutons (51%). In the CRcre;Ai9;Noc::eGFP mice, we found cells double labelled with GFP (Noc) and tdTomato (CR). Patch clamp recordings from these CR/Noc cells showed they exhibited characteristics of inhibitory interneurons, and that the majority of cells received monosynaptic C fiber input, including input from TRPV1-lacking afferents. These results suggest that CR islet cells are a major source of presynaptic inhibition on C^{MrgD} primary afferent.

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Poster

679. Somatosensation: Spinal Circuits

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FCT Norte 2020

Title: Primary afferent inputs to spinal lamina III antenna cells

Authors: E. C. FERNANDES[1], I. SANTOS[1], L. L. LUZ[1], E. KOKAI[2], D. HADHAZI[2], P. SZUCS[2], *B. V. SAFRONOV[1]
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Abstract: Dorsal horn of the spinal cord integrates and modulates primary afferent input to transmit it to supraspinal centers. Nociceptive myelinated Aδ and unmyelinated C fibers terminate in the superficial dorsal horn formed by laminae I-II, whereas thickly myelinated Aβ afferents mainly project to deeper laminae III-IV. There is in this region, however, a subset of neurons responding to both non-noxious and noxious stimuli whose role in nociceptive network is poorly understood. Here we did whole-cell patch-clamp recordings in an isolated spinal cord preparation with attached dorsal roots to characterize anatomically and electrophysiologically lamina III neurons receiving nociceptive input. Based on morphological features nine neurons in our sample have been identified as antenna cells. Their axons were located in laminae III-IV and, after crossing lamina II, also gave collateral branches in lamina I. Propriospinal collaterals in the lateral and dorsal fasciculus proprius were also present. Likewise, they had dorsal dendrites that projected as far as to lamina I (some branching extensively in the subpial white matter) and ventral dendrites distributed through laminae III-VII. These neurons showed mainly a tonic pattern of intrinsic firing (n=6). Antenna cells received monosynaptic primary afferent inputs from the low-threshold Aβ fibers (n=3), and in addition, from Aδ (n=7) and C (n=6) fibers. Thus, our results indicate that antenna cells are a specific group of lamina III neurons whose dendrites receive primary afferent input from Aβ, Aδ and C fibers, and axons relay information back to the superficial dorsal horn. Antenna cells represent an important element of the nociceptive neuron circuitry interconnecting deep and superficial dorsal horn.

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Poster

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HMRI grant

Title: PV-expressing cells in the mouse spinal dorsal horn gate the transmission of innocuous tactile input to lamina I

Authors: *A. DICKIE[1], K. A. BOYLE[1], T. YASAKA[2], V. E. ABRAIRA[3], A. L. ZIMMERMAN[3], D. D. GINTY[3], M. A. GRADWELL[4], R. J. CALLISTER[4], B. A. GRAHAM[4],

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Abstract: Chronic pain presents a major unmet clinical problem. One feature of chronic pain is the development of allodynia, where previously innocuous tactile stimuli are perceived as painful. We have shown that inhibitory spinal interneurons which express parvalbumin (PV) form axo-axonic synapses on to the central terminals of myelinated afferents, and have proposed that a loss of the inhibition they mediate could contribute to the development of allodynia following peripheral nerve injury. In this study, we aim to determine the synaptic relationship between low threshold mechanoreceptive (LTMR) afferent input and PV-cell mediated inhibition. We have used *in vitro* targeted recordings in spinal cord slices from PV^{Cre};Ai9 mice to show that stimulation of dorsal roots at Aδ strength elicits monosynaptic EPSCs in PV-expressing cells. We have used tissue from $Split^{Cre}$;Ai34 and $TrkB^{CreER}$;Ai35 mice to show that approximately 30% (mean 28.5% SD 14.9) and 35% (35.2% ± 6.3) of VGLUT1 inputs on to inhibitory PV neurons are derived from Aβ and Aδ hair afferents, respectively, and also find that central terminals of most Aβ and Aδ hair afferents receive contacts from inhibitory boutons that express PV (70.7% ± 8.1, and 80.1% ± 3.8, respectively). We also show that 27.9% (± 2.4) of VGAT boutons in contact with the dendrites of vertical cells in lamina IIi and III are derived from PV-expressing cells, and that 61.9% (± 17.2) of the VGLUT1 terminals that target these dendrites associate directly with PV/VGAT boutons. To determine whether PV cells mediate presynaptic inhibition of LTMRs and postsynaptic inhibition of vertical cells, we have also carried out *in vitro* optogenetic experiments in spinal cord slices from PV^{Cre};Ai32 mice. We find evidence of light-induced bicuculline-sensitive polysynaptic EPSCs in vertical cells, indicative of primary afferent depolarisation mediated by PV cells. We also find evidence of monosynaptic IPSCs that are sensitive to both bicuculline and strychnine, indicative of PV-cell mediated postsynaptic inhibition. Our findings provide anatomical and functional evidence that PV cells mediate both presynaptic inhibition of myelinated afferents that synapse on to vertical cells, and postsynaptic inhibition of the vertical cells themselves. We propose that decreased PV cell-mediated inhibition unmasks a circuit involving vertical cells. This enables LTMR input from lamina IIi and III to activate lamina I pain circuits, and could result in allodynia. Together, these findings identify PV interneurons as a target for therapeutic intervention to alleviate allodynic conditions.

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Poster

679. Somatosensation: Spinal Circuits

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Support: UMN-ACH, The Winston and Maxine Wallin Neuroscience Discovery Fund

NINDS F32 NS100438

Title: Analysis of spinothalamic tract neuron connectivity in the lumbar enlargement of the mouse spinal cord

Authors: *A. G. SKORPUT, M. S. RIEDL, C. N. HONDA, L. VULCHANOVA
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Abstract: Local circuitry in the dorsal horn of the spinal cord remains incompletely understood yet the plasticity of these circuits and their involvement in the development and maintenance of chronic pain states are increasingly clear. Among the remaining questions is the identity and relative abundance of interneuron subtypes that synapse onto spinothalamic tract (STT) projection neurons. As the ascending output neurons for nociceptive information flowing within intraspinal sensory circuits, the balance of synaptic inhibition verse excitation upon STT neurons is largely responsible for determining whether a given somatosensory stimulus will be perceived as noxious. Utilizing viral (AAV9) based retrograde tracing methods, we have labeled STT neurons in the lumbar enlargement with tdTomato. Application of multiphoton confocal imaging and CLARITY based tissue clearing methods has enabled visualization of STT neurons throughout the depth of the spinal cord dorsal horn along the full length of the intact lumbar enlargement. This viral tracing method labels both superficial (Layer I, IIo) and deep (Layer V) STT projection neurons, presumably representing both nociceptive specific and wide dynamic range populations. These methods are being expanded to include ΔG-Rabies based monosynaptic tracing methods to allow fluorescent labeling of interneurons with presynaptic input to STT neurons. Subsequent immunohistochemical analysis will allow identification and quantification of known dorsal horn interneuron subtypes and categorization as either inhibitory or excitatory in nature. Future experiments will examine changes to this connectivity in animal models of chronic pain. Additionally, these methods may provide a route for genetic manipulation of STT projection neurons and their presynaptic input neurons for integrated neuroanatomical and physiological analyses in naïve and chronic pain animals.

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Poster

679. Somatosensation: Spinal Circuits

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NASU Nanotechnology

Title: Electrophysiological responses of lamina X spinal cord neurons to primary afferent stimulation

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Abstract: The area around the central canal (or lamina X) is the most enigmatic lamina of the spinal cord. It is established that nociception, autonomic regulation and modulation of motoneuron output are mediated by lamina X neurons. Nevertheless, their electrophysiological properties and functional connectivity are largely unknown. Using oblique LED illumination we developed a technique allowing visually guided patch clamp of lamina X cells combined with simultaneous stimulation of dorsal roots. Cell-attached recordings from the lamina X neurons of L4-L5 lumbar segments showed that 70% of these cells spontaneously generate action potentials (APs), though just 43% of these neurons generated APs in response to supramaximal (C-fiber) stimulation of L4 or L5 dorsal root. The same stimulation in the whole cell patch clamp configuration induced responses in more than 90% of neurons, indicating that in a half of lamina X neurons nociceptive stimulation results in inhibitory or subthreshold excitatory postsynaptic currents. Interestingly, the percentage of neurons responding to a low threshold A-fiber stimulation was much lower (38%), suggesting that lamina X is preferentially innervated by C-fiber primary afferents. Analysis of responses to dorsal root stimulation revealed the following. First, the responses were quite diverse, several (5-7) various types could be distinguished. The most notable one was characterized by a strong spontaneous synaptic activity superimposed on a prolonged (up to several seconds) inward current. We hypothesize that neurons exhibiting such response might serve as integrators of network activity. Second, the majority of responses had a polysynaptic component, though in at least 25% of neurons monosynaptic responses (determined by high reproducibility and low jittering) were found. Third, in 25% of lamina X neurons polysynaptic inhibitory currents were observed upon supramaximal stimulation indicating lamina X neurons are under substantial inhibitory control. Finally, low frequency (1Hz) dorsal root stimulation caused long term depression (LTD) of monosynaptic excitatory responses in 15% of tested neurons. We conclude that lamina X neurons preferentially receive inputs from C-fiber

primary afferents, stimulation of which elicits AP generation in significant proportion of these cells. A marked percentage of neurons displaying inhibitory inputs and LTD suggests that lamina X circuitry reveals the properties that might be protective during noxious C-fiber activation.

Disclosures: V. Krotov: None. **A. Tokhtamysh:** None. **P. Belan:** None. **N. Voitenko:** None.

Poster

679. Somatosensation: Spinal Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 679.18/DD10

Topic: D.02. Somatosensation

Support: KAKENHI 15K08673

Title: Plant-derived compound-induced outward current in adult rat spinal substantia gelatinosa neurons and the chemical structure of the compound

Authors: T. YU, *T. FUJITA, C. WANG, R. SUZUKI, N. MAGORI, F. YANG, E. KUMAMOTO
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Abstract: Many of endogenous analgesics such as opioids, nociceptin, noradrenaline, serotonin and adenosine produce a membrane hyperpolarization in spinal dorsal horn lamina II (substantia gelatinosa; SG) neurons that play a pivotal role in regulating nociceptive transmission from the periphery. Transient receptor potential ankyrin-1 (TRPA1) channels receive nociceptive cold stimuli in the peripheral terminal of dorsal root ganglion neuron while those in the central terminal of the neuron in the SG play a role in modulating nociceptive transmission. We have previously reported in a spinal cord slice that the central terminal TRPA1 channels in the SG are activated by a variety of plant-derived compounds. Among the compounds, there are allyl isothiocyanate, cinnamaldehyde, allicin, zingerone, citral, eugenol, carvacrol and thymol. The latter three compounds of them produced a membrane hyperpolarization while the others did not. It is possible that such a hyperpolarization is involved in antinociception produced by the intraperitoneal administration of the plant-derived compounds. In order to reveal what chemical structures of the plant-derived compounds are important in the production of the hyperpolarization, we examined the effects of guaiacol, vanillin, vanillic acid and *p*-cymene, all of which are similar in chemical structure to eugenol, carvacrol and thymol, on holding current and spontaneous excitatory transmission at -70 mV by applying the whole-cell patch-clamp technique to SG neurons in adult rat spinal cord slices. All of guaiacol, vanillin, vanillic acid and *p*-cymene hardly affected the frequency and amplitude of spontaneous excitatory postsynaptic current. Vanillin and *p*-cymene produced an inward and outward current, respectively, while the other compounds did not change holding currents. In all neurons tested, vanillin at 5 mM elicited

an inward current. On the other hand, *p*-cymene at 2 mM produced an outward current in 24 % of the neurons examined. Comparison of the chemical structure of eugenol with those of guaiacol, vanillin and vanillic acid indicates an importance of -$CH_2CH=CH_2$ bound to eugenol in producing the outward current. Furthermore, the observation that *p*-cymene produces an outward current having peak amplitude much smaller than those of carvacrol and thymol suggests a role of -OH bound to thymol or carvacrol in the production of the outward current. In conclusion, a membrane hyperpolarization produced in SG neurons by some of plant-derived compounds activating central terminal TRPA1 channels requires a functional group bound to the compounds, such as -$CH_2CH=CH_2$ and -OH.

Disclosures: **T. Yu:** None. **T. Fujita:** None. **C. Wang:** None. **R. Suzuki:** None. **N. Magori:** None. **F. Yang:** None. **E. Kumamoto:** None.

Poster

679. Somatosensation: Spinal Circuits

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Program#/Poster#: 679.19/DD11

Topic: D.02. Somatosensation

Support: KAKENHI 15K08673

Title: Effects of orexin A and orexin B on spontaneous synaptic transmission in adult rat spinal substantia gelatinosa neurons

Authors: *C. WANG, T. FUJITA, N. MAGORI, R. SUZUKI, F. YANG, E. KUMAMOTO
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Abstract: Orexin (hypocretin) A and orexin B originating from the hypothalamus inhibit nociceptive transmission in the spinal dorsal horn. We have previously reported that orexin B produces an inward current at -70 mV and increases the frequency of spontaneous excitatory postsynaptic current (sEPSC) with no change in its amplitude in about a half of the adult rat spinal dorsal horn lamina II (substantia gelatinosa; SG) neurons examined. The SG neurons play a pivotal role in regulating nociceptive transmission from the periphery. The present study further examined the effects of orexin B and also orexin A on holding currents, sEPSCs and spontaneous inhibitory postsynaptic currents (sIPSCs; recorded at 0 mV) in SG neurons by using the whole-cell patch-clamp technique in adult rat spinal cord slices. As with orexin B, orexin A (0.05 μM) produced either inward current or increase in sEPSC frequency that was not accompanied by a change in its amplitude. These orexin A activities were concentration-dependent. The proportion of the neurons sensitive to orexin A was larger than that of orexin B. In the same neurons, the activities of orexin A were not different in extent from those of orexin B. The orexin A and orexin B activities were repeated and resistant to a voltage-gated Na^+-

channel blocker tetrodotoxin. The orexin B effects were inhibited by orexin-2 but not orexin-1 receptor antagonist (JNJ10397049 and SB334867, respectively), while the orexin A ones were inhibited by both SB334867 and JNJ10397049 albeit the latter inhibition was much smaller in extent than the former one. With respect to inhibitory transmission, orexin B (0.05 μM) increased the frequency and amplitude of glycinergic sIPSC in some 70 % of the neurons tested. This orexin B activity was repeated and sensitive to tetrodotoxin. A similar enhancement of glycinergic sIPSC was produced by orexin A (0.05 μM). These results indicate that orexin A and orexin B produce a membrane depolarization in SG neurons and increase the spontaneous release of L-glutamate onto SG neurons from nerve terminals by activating orexin-1 and orexin-2 receptors, both of which actions result in an increase of the excitability of the neurons. Such an increase in neuronal excitability produces action potentials, leading to an enhancement of glycinergic spontaneous inhibitory transmission. It is suggested that antinociception produced by orexin A and orexin B is mediated by glycinergic spontaneous inhibitory transmission enhancement occurring as a result of an increase in the excitability of SG neurons by activating orexin-1 and orexin-2 receptors.

Disclosures: C. Wang: None. **T. Fujita:** None. **N. Magori:** None. **R. Suzuki:** None. **F. Yang:** None. **E. Kumamoto:** None.

Poster

679. Somatosensation: Spinal Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 679.20/DD12

Topic: D.02. Somatosensation

Support: R01- DA015353

Title: Characterization of DMT-DALDA peptide (2): Study with continuous intrathecal infusion

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Abstract: DMT-DALDA (Dmt - 2',6'-dimethyl tyrosine) is an opioid agonist with high selective affinity for the mu-opioid receptor. Work with bolus intrathecal delivery has shown it to be extremely potent, with an efficacious intrathecal dose in the rat of 1-3 pmol as compared to 30 nmol for morphine. Further, consistent with resistance to peptidases, its peptidic structure and charge, it has duration of action that resembles hydrophilic molecules such as morphine. In the present study we characterized the efficacy and side effect profile of DMT DALDA given by

continuous intrathecal infusion to assess side effect profile, tolerance and dependence. Adult male Sprague Dawley rats were prepared with chronically implanted intrathecal catheters and osmotic mini-pumps to deliver vehicle (saline), DMT-DALDA or morphine. Hind paw thermal escape latencies were assessed using a Hargreaves-like device along with systematic assessment of motor function. In addition, effects upon intraplantar formalin-evoked flinching were examined. The following observations were made: i) Intrathecal infusion of 3-30pmol/µl/h of DMT-DALDA or 10 nmol/µL/h of morphine over 7 days resulted in a dose-dependent increase in thermal escape latency. The maximum effect was observed between 1 and 4 days after start of infusion with no motor dysfunction (preserved cornea, blink, placing and stepping, no straub tail). At 100pmol/µl/h or more, DMT-DALDA resulted in motor dysfunction. ii) In separate experiments, DMT-DALDA (20pmol/ 0.5µl/h for 14 days) displayed recovery to baseline by day 10 and below baseline by days 12-14. iii) On days 2-4 of DMT DALDA infusion, the pain antagonist naloxone, but not the delta preferring antagonist naltrendole, antagonized the analgesic action of DMT DALDA. iv) Formalin test on DMT-DALDA Infusion day 1 showed significant analgesia in phases 1 and 2. On day 6 of infusion there was minimal effect, while on day 13, there was an increase in flinching, suggesting tolerance and opioid-induced hyperalgesia. v) On days 7 and 14 of infusion Naloxone resulted in prominent withdrawal signs indicating dependence and withdrawal. These data suggest that DMT-DALDA is a potent, spinally active agonist with a propensity to produce tolerance and dependence.

Disclosures: S. Kokubu: None. **K. Eddinger:** None. **S. Yamaguchi:** None. **P.W. Schiller:** None. **T.L. Yaksh:** None.

Poster

679. Somatosensation: Spinal Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 679.21/DD13

Topic: D.02. Somatosensation

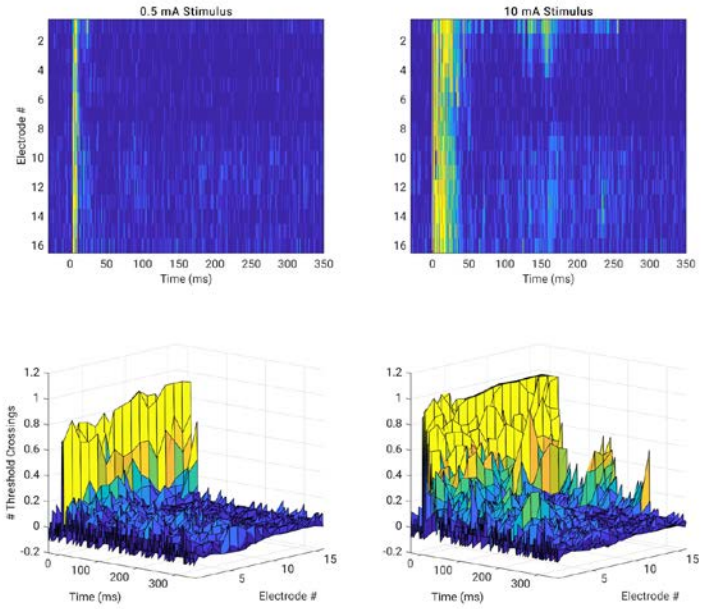
Support: BBSRC DTP

Title: Multi-laminar electrophysiological recordings in the spinal dorsal horn

Authors: *C. M. GREENSPON[1], I. M. DEVONSHIRE[2], L. DONALDSON[3], V. CHAPMAN[3], G. J. HATHWAY[1]
[1]Sch. of Life Sci., [2]Biol. Support Unit, [3]Sch. of Life Sciences/Arthritis Res. UK, Univ. of Nottingham, Nottingham, United Kingdom

Abstract: Electrophysiological measurements of neuronal activity in the spinal dorsal horn (DH) have made significant contributions to our understanding of the role of the DH in peripheral sensation. The majority of studies have used single unit techniques and focused on wide dynamic

range neurons in lamina V of the DH. Recent studies have highlighted that interactions between laminae are crucial for the integration of both nocuous and innocuous sensory information, which cannot be measured with traditional recording techniques. Here we describe the use of multi-electrode arrays (MEAs) to simultaneously record activity from all laminae of the DH. MEAs were inserted into lumbar 5 of the DH in terminally anaesthetised adult Sprague-Dawley rats to record from laminae I-V. Multi-unit activity and local field potentials were recorded at each electrode. Electrical stimuli of varying intensity (0.1 - 10 mA; 2 ms), duration (5 mA; 200 μs - 20 ms), and frequency (0.1 & 0.5 Hz) were applied to the ipsilateral hindpaw and evoked spinal responses recorded. Effects of intrathecal saline and morphine (5ng/50μl) on evoked responses were recorded. Offline processing was performed using Matlab and Prism.
MEAs quantified fibre electrical thresholds as: Aβ (0.5 mA, $p < 0.0001$ - compared to sub-threshold stimulation); Aδ (1 mA, $p = 0.0054$); C-fibres (5 mA, $p < 0.0001$), post-discharge activity was evident at 5 mA stimulation ($p < 0.0001$). All fibre latencies, similarly, showed encoding of stimulus duration. Depth specific innervation profiles were detected for both C-fibre evoked and post-discharge activity in response to changing stimulus amplitude and duration. Increased firing rate in response to high frequency stimulation was significant (slope: -0.014 at 0.1 Hz, $p = 0.77$; 0.793 at 0.5 Hz, $p < 0.0001$) in the deeper laminae, but not in the superficial or intermediate laminae. Morphine caused significant inhibition in C-fibre activity in the superficial (64% reduction, $p = 0.019$) and deep (72% reduction, $p = 0.029$) laminae. Thus MEAs are an efficient and powerful tool for the study of DH activity and networks.



Disclosures: **C.M. Greenspon:** None. **I.M. Devonshire:** None. **L. Donaldson:** None. **V. Chapman:** None. **G.J. Hathway:** None.

Poster

679. Somatosensation: Spinal Circuits

Location: Halls A-C

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Program#/Poster#: 679.22/DD14

Topic: D.02. Somatosensation

Title: Neural effects in lactating rats produced by suckling in a somatic reflex

Authors: *M. A. LARA GARCIA[1], Y. CRUZ[2], O. LARA GARCIA[3], P. PACHECO[4]
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Abstract: The milk ejection involves endocrine and neural processes. The last are represented by activation of sensory receptors of the mammary glands, likewise those of the surrounding skin. During suckling, pups activate these receptors through nipple swallowing and by forelimbs movement. Piloerection presence would imply an autonomic reflex activation and probably other reflexes activation such as alert reaction. In the present study, we analyzed if the somatic reflex represented by the tail flick is also involved during suckling. Measurement of tail flick latency (TFL) was performed using lactating rats during the three thirds of lactation. TFL was obtained before, during, and after suckling period. It was observed that TFL was reduced as suckling period went on, reaching its lowest value after 30 min of suckling; moreover, this pattern is different depending on the third of lactation. Regardless presence or absence (empty gland or milk duct blockage) of milk ejection there was no difference in TFL measured 30 min after suckling had started; however, TFL had a different pattern of progressive increment after suckling. Additionally, we found that as compared to dorsum skin mechanical stimulation, mammary gland stimulation showed a significant reduction in TFL. Present results showed that during lactation, sensory input originated by the suckling stimulation produces rapid and strong neuromodulatory plastic changes in the lumbosacral spinal cord.

Disclosures: M.A. Lara Garcia: None. **Y. Cruz:** None. **O. Lara Garcia:** None. **P. Pacheco:** None.

Poster

680. Somatosensory Cortex

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Program#/Poster#: 680.01/DD15

Topic: D.04. Somatosensation: Touch

Support: ANR-09-JCJC- 0028-01

Title: Cortical dynamics in the mouse during a tactile-detection task

Authors: P. LE MERRE[1,3], V. ESMAEILI[1], C. C. H. PETERSEN[1], P. SALIN[3], *S. CROCHET[2,3]
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Abstract: Functional coupling between cortical areas through synchronized activities in different frequency bands is thought to play an important role in various cognitive process, and is strongly affected by behavioral or mental states. In a recent study (Fernandez et al., 2016), we found that the cortical activity in the cortex of the awake mouse is dominated by long-range coherence in a low-frequency band (LF, 0.5-10 Hz), with particularly strong coherence between the medial prefrontal cortex (mPFC) and the parietal associative cortex (PtA), and between these two areas and other cortical areas. On the contrary, long-range cortical coherence dropped during slow-wave sleep in the LF band, despite a large increase in amplitude in this frequency band. In the present study, we investigated the cortical dynamics and long-range interactions in mice involved in a goal directed task requiring sustained attention. Mice were implanted with 6 chronic electrodes to record local field potential and were then trained in a whisker-based sensorimotor detection task (Sachidhanandam et al., 2013). The targeted cortical areas included sensorimotor areas directly involved in processing the whisker sensory stimulus: the whisker primary and secondary somatosensory areas (wS1 and wS2) and the whisker primary motor area (wM1). We also recorded from associative and higher-order areas: mPFC, PtA and the dorsal CA1 region of the hippocampus (dCA1). Overall, the cortical spontaneous activity in mice performing the detection task did not differ markedly from that of mice not involved in a task (spontaneous wakefulness), with periods of high-amplitude, LF activities in sensorimotor areas (wS1, wS2 and wM1) that alternated with periods of low-amplitude, high-frequency activities correlated with motor activity. Delta activity dominated in mPFC while theta activity was more prominent in PtA and dCA1. Interestingly, we observed a strong modulation of cortical activities within behavioral sessions: over single sessions, LF activity increased gradually in most cortical areas with a pronounced increase in wS2 and wM1. This change in cortical activity correlated with a change in behavioral performance with a progressive decrease in false-alarm rate and increase in reaction time, until the mice stopped performing due to lack of motivation. The increase in LF cortical activity, was accompanied by a decrease in coherence that was particularly pronounced between mPFC and PtA, and the sensorimotor areas (wS1, wS2 and wM1). Together, our results support the idea that high functional coupling between distant areas in the LF band may be a marker of high vigilance level and/or attentional states.

Disclosures: **P. Le Merre:** None. **V. Esmaeili:** None. **C.C.H. Petersen:** None. **P. Salin:** None. **S. Crochet:** None.

Poster

680. Somatosensory Cortex

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 680.02/DD16

Topic: D.04. Somatosensation: Touch

Title: Layer, cell-type and pathway-specific thalamocortical input to mouse primary somatosensory barrel cortex

Authors: *B. S. SERMET[1], T. B. ORAM[2], O. YIZHAR[3], C. C. PETERSEN[4]
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Abstract: In the mouse whisker system, sensory information is relayed to the primary somatosensory barrel cortex by two major thalamic nuclei, the ventral posterior medial nucleus (VPM) and the posterior medial nucleus (POM). While the axonal innervation pattern of these two nuclei has been studied anatomically in some detail, their synaptic input to distinct cell-types across different layers in barrel cortex is incompletely understood. We used the specificity of optogenetics to selectively stimulate axons from VPM or POM, and we measured the evoked excitatory postsynaptic potentitals *in vitro* whole-cell patch-clamp recordings. VPM or POM was infected *in vivo* with an adenoassociated virus encoding the light-gated cation channel channelrhodopsin (ChR2). Synaptic input onto individual neurons of the barrel cortex was recorded in brain slices *in vitro* by activating the ChR2-expressing thalamic axons with blue light. We first measured thalamic inputs onto excitatory neurons across all layers of the barrel cortex, finding that the biggest inputs appeared to largely colocalise with the anatomical innervation pattern. Anatomically, VPM preferantially innervates L4, deep L3 and the L5B/6A border, and, functionally, we found that the biggest input was observed in L4, followed by L2/3. Anatomically, POM innervates L5A and L1, and, functionally, we found the biggest input in L5A, followed by L2/3. In ongoing experiments, we are measuring the input from POM and VPM across cortical layers onto three distinct classes of GABAergic neurons, expressing parvalbumin, somatostatin or vasoactive instestinal peptide. Our results begin to provide a more complete understanding of the distribution of thalamic input to specific cell-types across the layers of the mouse barrel cortex.

Disclosures: **B.S. Sermet:** None. **T.B. Oram:** None. **O. Yizhar:** None. **C.C. Petersen:** None.

Poster

680. Somatosensory Cortex

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 680.03/DD17

Topic: D.04. Somatosensation: Touch

Title: Reward-based learning drives recruitment of the medial prefrontal cortex and the dorsal hippocampus during a goal-directed sensorimotor task in the mouse

Authors: *P. F. LE MERRE[1], V. ESMAEILI[1], P. A. SALIN[2], C. C. PETERSEN[1], S. CROCHET[1]
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Abstract: Sensory perception leading to goal-directed behavior involves multiple, spatially-distributed and inter-connected cortical areas. It has been hypothesized that sensory information flows from primary sensory areas encoding mainly the features of the stimulus, to higher-order areas encoding the valence of the stimulus. To investigate sensory signals at high time-resolution, we recorded sensory evoked potentials (SEPs) from different cortical areas in mice performing a whisker-based sensory detection task (Sachidhanandam et al., 2013). Mice were chronically implanted with 6 high-impedance local field potential (LFP) electrodes and were either trained to lick a spout immediately after a brief whisker deflection to obtain a reward (detection task), or were exposed to the same whisker stimulus not associated with reward (neutral exposition). In trained mice, whisker deflection evoked SEPs in all recorded areas with latencies increasing from primary somatosensory barrel cortex (wS1) to secondary somatosensory cortex (wS2), the whisker motor cortex (wM1), the parietal association cortex (PtA), the dorsal hippocampus (dCA1) and the medial prefrontal cortex (mPFC). The amplitude of SEPs was significantly larger in Hit trials compared to Miss trials in all areas except wS1. Pharmacological and optogenetic inactivation experiments demonstrated that activity in wS1, wS2, dCA1 and mPFC was required for task execution. The amplitude of the SEP in dCA1 or mPFC increased in correlation with behavioral performance, and whisker deflection did not evoke a SEP in dCA1 or mPFC of neutral exposition mice. Sensory responses in mPFC were acquired during reward-based sensorimotor learning and are essential for task execution. In order to further examine neuronal activity in mPFC, we performed high-density extracellular action potential recordings in mPFC of mice trained in the detection task and in mice after neutral exposition. We found that the whisker stimulus evoked an overall increase in activity of putative excitatory cells in mPFC during the detection task, with stronger evoked activity for Hit trials than for Miss trials. In agreement with LFP recordings, no sensory evoked response was observed in the spiking activity of mice during neutral exposition. Our results suggest the

hypothesis that behaviorally irrelevant stimuli evoke activity mainly limited to sensory areas (wS1, wS2 and wM1), whereas behaviorally relevant sensory stimuli additionally recruit dCA1 and mPFC that are critically involved in task execution.

Disclosures: **P.F. Le Merre:** None. **V. Esmaeili:** None. **P.A. Salin:** None. **C.C. Petersen:** None. **S. Crochet:** None.

Poster

680. Somatosensory Cortex

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Program#/Poster#: 680.04/DD18

Topic: D.04. Somatosensation: Touch

Support: Swiss National Science Foundation

European Research Council

Title: Optical mapping of large-scale cortical sensorimotor activity in awake head-restrained mice

Authors: M. AUFFRET, *C. C. PETERSEN
École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

Abstract: Optical methods are beginning to provide important information about the spatiotemporal distribution and dynamics of neuronal activity in awake behaving mice. Transgenic animals allow both optical control of neuronal activity through optogenetic actuators, and optical measurement of neuronal activity through imaging genetically-encoded calcium-sensitive fluorescent probes. Those two complementary methods provide the opportunity to optically map the large-scale structure of neuronal network activity during behavior. In a previous study (Auffret et al., 2017) we investigated whisker motor maps evoked by optogenetically stimulating the dorsal sensorimotor cortex of awake mice expressing channelrhodopsin-2 in diverse brain areas. Interestingly, whisker movements were evoked by optical stimulation of multiple broadly distributed cortical regions. Here, we further investigate the organization of dorsal sensorimotor cortex through imaging of awake head-restrained transgenic mice expressing the genetically-encoded calcium-sensor GCaMP6f (Dana et al., 2014). We train mice to detect whisker stimuli and to lick a spout in order to get a reward. In ongoing experiments, we find a rapid response shortly after stimulus onset in primary somatosensory cortex for both hit and miss trials. In hit trials, we observe rapid spread of activity to frontal regions, followed by long-lasting brain-wide activity during a second phase. Our data point to a rich interaction between cortical areas that could play a key role in performing the task. Further experiments and analyses will focus on mapping distinct aspects of the neuronal activity

during different behavioral epochs involved in sensory-motor transformation and decision-making.

References:
Auffret M, Ravano VL, Rossi GMC, Hankov N, Petersen MFA, Petersen CCH (2017) Optogenetic stimulation of cortex to map evoked whisker movements in awake head-restrained mice. Neuroscience, doi: 10.1016/j.neuroscience.2017.04.004
Dana H, Chen TW, Hu A, Shields BC, Guo C, Looger LL, Kim DS, Svoboda K (2014) Thy1-GCaMP6 transgenic mice for neuronal population imaging in vivo. PLoS One 9: e108697.

Disclosures: M. Auffret: None. **C.C. Petersen:** None.

Poster

680. Somatosensory Cortex

Location: Halls A-C

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Program#/Poster#: 680.05/DD19

Topic: F.08. Biological Rhythms and Sleep

Support: German Research Foundation (SFB-1089)

Human Frontier Science Program

Title: Diverse types of interhemispheric membrane potential correlation between somatosensory cortices of awake mice

Authors: *Y. A. KATZ, K. COHEN-KASHI MALINA, I. LAMPL
Neurobio., Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Synchronized neuronal activity is a major hallmark of cortical physiology and it is suggested to contribute in various cortical functions, including enhancing flow of information, coding, and plasticity. Whereas high correlation in nearby cells is expected due to common inputs, correlation among distant cells is less well understood. A particularly striking case is that of interhemispheric correlations which are suggested to arise from transcallosal projections connecting homologous areas. However, these connections cannot fully explain the positive nature of these correlations since they are known to mediate slow interhemispheric inhibition. Interhemispheric correlations were previously examined using extracellular and imaging techniques, but these methods are limited when investigating subthreshold mechanisms and cell type specificity of interhemispheric relationships. Hence greater insight into these questions can be obtained by examining the membrane potential correlations across hemispheres, which have thus far remained unknown in awake animals. Moreover, little is known about the relationships between interhemispheric correlation and brain-state. Using bilateral paired intracellular recordings from the somatosensory cortices of awake mice during ongoing activity, we found

diverse interhemispheric correlations. In the infraslow frequency range (<1 Hz) membrane potentials of some pairs were positively correlated whereas in other pairs we recorded profound negative correlations. Filtering the recordings above 1Hz revealed large diversity in the magnitude of averaged correlations, but they were always positive. Importantly, close examination of subthreshold activities in both hemispheres indicated that rapid fluctuations between Up and Down membrane potential states, thought to reflect rapid local network dynamics, were correlated across hemispheres with near millisecond precision. Moreover, in these cases spike triggered average of membrane potential across hemispheres revealed rapid common input and significant correlation in firing. Finally, slow changes in the magnitude of interhemispheric synchronization were related to physiological signals. In some pairs changes in infraslow correlation were related to pupil area and animal movements, which decreased when pupil size increased or during locomotion. The diverse types of interhemispheric subthreshold correlation suggests that interactions across hemispheres play multiple functions in behavior, and that they can be modulated by distinct behavioral states.

Disclosures: Y.A. Katz: None. **K. Cohen-Kashi Malina:** None. **I. Lampl:** None.

Poster

680. Somatosensory Cortex

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 680.06/DD20

Topic: D.04. Somatosensation: Touch

Title: Time-dependent population responses underlying spatial representation in the primary somatosensory cortex: The cortical body map revisited

Authors: *J. CORBO, Y. ZENNOU AZOGUI, C. A. XERRI, N. CATZ
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Abstract: The sensory systems have to make sense out of ambiguous and fragmentary inputs that come from our sensors. The meaningful ‘whole’ that one perceives is made out of ‘bits’ bounded together. The rules that govern this reconstruction process may be inscribed in the computational routine of the neural networks that process sensory inputs. The illusion of tactile “saltation” suggests that successive brief tactile stimulations delivered on two different locations are felt as single object hoping linearly between the two cutaneous regions. Psychophysical exploration of this phenomenon allowed to unveil its basic rule : the distance perceived between two successive tactile stimuli is proportional to the interstimulus time interval (ISI). As the primary somatosensory cortex (SI) contains a topographically organized representation of the body cutaneous surfaces, we hypothesized that stimuli representation within this map undergoes spatial distortion dependent upon the ISI between two distant tactile stimuli. In order to test this hypothesis, we recorded the responses of about 500 SI neurons in anesthetized rats, while

delivering sequences of cutaneous stimuli on adjacent or non-adjacent digits (from digit 2 to 5), with ISI ranging from 0 to 400ms. During single-digit stimulation, S1 units displayed a "preferred" response consistent with the topographic organization. When the same stimulation was preceded by another one on a different digit, those discharges either increased or decreased as if SI neurons' selectivity changed according to their "recent stimulation history". Considered alone, the discharge of individual cells was unable to account for the time-space distortion. However, the spatial information embedded in the population response to the second stimulus was shifted toward the location of the first one, leading to a reduction in representational distance between two successive stimuli. As suggested by the "saltation" illusion, representation of space in SI is time-dependent. This dynamical change in SI population response can be thought of as a neural substrate of the perceptual time-space transformation, and challenges the classical view of the cortical cutaneous body map as a simple spatial reference frame for stimulus location.

Disclosures: J. Corbo: None. **Y. Zennou Azogui:** None. **C.A. Xerri:** None. **N. Catz:** None.

Poster

680. Somatosensory Cortex

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 680.07/DD21

Topic: D.04. Somatosensation: Touch

Title: Detailed somatotopy of the rat trunk sensory cortex

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Abstract: While there exists extensive information about the somatotopic organization of the rat forelimb and hindlimb sensory cortex, very little is known about the details of trunk sensory cortex. Knowledge of the details of somotatopic organization is important for studies of neurological injury or disease where the representation of these maps change in response to the injury and in response to therapy to restore function. The trunk cortex is especially important for studying the development of at-level pain after mid-thoracic spinal cord injury. Importantly for the trunk somatotopic organization, there is also limited knowledge about thoracic dermatomes. In this study, both the thoracic dermatomes and the somatotopic organization of the cortex in naïve rats were evaluated. Naive female Sprague Dawley rats were anesthetized with 1.5 g / kg urethane and a grid of 128 equally spaced squares were drawn on the dorsal aspect of the shaved trunk. To identify the mid-thoracic dermatomes, the mid-thoracic vertebrae and the dorsal root ganglia (DRGs) were exposed. A tungsten microelectrode was inserted into each DRG and single unit neurons were identified. Upon identification, the animal's skin was lightly stimulated with a

wooden probe and the cell's receptive field (RF) was determined in relation to the body grid. The union of the receptive fields of all cells found within a single DRG were used to define the DRG dermatome. To identify the somatotopy within the trunk sensory cortex, a craniotomy exposing the trunk representation as well as surrounding regions was performed. Dura was removed, and a tungsten microelectrode was slowly lowered through the cortex in one of several pre-defined locations. Single unit neurons and RFs of responsive neurons were identified in a similar manner as the dermatome map. In a subset of animals, local field potentials (LFPs) were recorded using electrical stimulation to the trunk. Our results identify the mid-thoracic dermatomes and support a somatotopic organization of the trunk sensory cortex in the rat, with a caudal to rostral sensory receptive field orientation over the medial to lateral cortical area, and a dorsal to ventral receptive field orientation over the caudal to rostral cortical area. LFP recordings show the cortical extent of trunk afferent information. These results provide a basis to study cortical reorganization of the trunk sensory cortex after injury or disease.

Disclosures: G.H. Blumenthal: None. **B. Nandakumar:** None. **K.A. Moxon:** None.

Poster

680. Somatosensory Cortex

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Topic: D.04. Somatosensation: Touch

Support: Fondecyt 1170027

VID-ENL-2016

Title: Layers and columns are also present in the somatosensory avian pallium

Authors: M. FERNANDEZ, R. REYES-PINTO, C. NORAMBUENA, *J.-C. LETELIER, J. MPODOZIS
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Abstract: One of the main components of the avian pallium corresponds to a dorsal intraventricular protrusion known as dorsal ventricular ridge (DVR). The DVR is constituted by two apposed cellular masses: the internal nidopallium (N) and the more external mesopallium (M). The internal most aspect of the N contains discrete areas receiving auditory (field L2), tectovisual (entopallium) and trigeminal (nucleus basorostralis, B) ascending projections. While the former two areas receive its sensory inputs from nuclei of the dorsal thalamus, the latter receive afferents directly from the brainstem trigeminal complex. Dorsally adjacent to each of these areas there is a nidopallial strip termed intermediate nidopallium (NI), which is limited dorsally by a portion of the ventral division of the mesopallium (MV). Previous studies have

shown that the auditory as well as the tectovisual regions of the DVR are organized according to a "laminar/columnar" arrangement, in which cells located in homotopic positions in each of these layers are reciprocally linked by an interlaminar local loop of axonal processes. Whether this type of organization extends also to the trigemino-recipient DVR is at present not known. We investigate this latter question by placing minute injections of neural tracers into selected locations of vital slices of the chicken telencephalon. After a prudent survival period, the slices were resectioned, reacted with DAB/Ni and counterstained with Giemsa. We found that neurons of the nucleus basorostralis establish reciprocal, columnar and homotopically organized projections with cells located in its overlying MV region. "Colum forming" axons originated in B and MV terminate also into the NI in a restricted manner. NI cells, in turn, send efferent projections mainly to other pallial areas. Furthermore, we found that besides of its intrapalial connectivity, B originates substantial, non-topographic projections to the underlying portion of the lateral striatum. This latter feature has been describe previously in the tectovisual, but not in the auditory, DVR. We conclude that all sensory areas of the DVR are organized according to a common neuroarchitectonic motif, which bears a striking resemblance to that of the interlaminar circuits of sensory cortices of mammals. This pattern seems to be determined by morphogenetic processes proper to the DVR, since it is not affected by the source of origin of the sensory afferents impinging upon a particular area.

Disclosures: **M. Fernandez:** None. **R. Reyes-Pinto:** None. **C. Norambuena:** None. **J. Letelier:** None. **J. Mpodozis:** None.

Poster

680. Somatosensory Cortex

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Topic: D.04. Somatosensation: Touch

Support: NMRPD1E1212

CMRPG3C0464

CMRPG5D0163

Title: Neuronal processing of cross-finger motion integration in the primary somatosensory cortex

Authors: *Y.-P. CHEN[1,2], J.-J. HUANG[2], C.-I. YEH[3], Y.-C. PEI[2,1]
[1]Chang Gung Univ., Taoyuan City, Taiwan; [2]Dept. of Physical Med. and Rehabil., Chang Gung Mem. Hosp., Taoyuan, Taiwan; [3]Natl. Taiwan Univ., Taipei, Taiwan

Abstract: Dynamic object manipulation involves tactile motion perceived through multiple fingerpads. Neuronal tuning properties to direction and orientation in the primary somatosensory (S1) cortex has been delineated but the integration of tactile motion across fingers is not yet known. To this end, we used a multi-digit tactile motion stimulator with scanning balls engraved with square-wave gratings to present tactile motion to two nearby fingerpads and recorded the neuronal responses in areas 3b, 1 and 2 of anesthetized monkeys using multi-channel microelectrode arrays. Specifically, either one (one-finger condition) or both (two-finger condition) of the two fingers were presented with the stimuli, yielding a variety of combination of stimulus direction presented to the two fingers. We found that a majority of motion-sensitive neurons have two-finger receptive fields. Comparing the activities obtained in one- and two-finger conditions in motion-sensitive neurons, 26% and 45% of neurons showed enhancement or suppression of direction/orientation selectivity in the two-finger condition, respectively, while, in the remaining neurons, the responses of two-finger condition is simply a weighted sum of responses observed in the one-finger condition. Furthermore, the motion integration observed in the two-finger condition was mainly mediated by a nonlinear suppression of neuronal activities. These results indicate that motion integration across fingers is commonly observed in S1 neurons and can be accounted for by nonlinear suppressions of convergent inputs emanating from two fingers, yielding a novel non-classical receptive field property that is first reported in primate S1.

Disclosures: **Y. Chen:** None. **J. Huang:** None. **C. Yeh:** None. **Y. Pei:** None.

Poster

680. Somatosensory Cortex

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Topic: D.04. Somatosensation: Touch

Support: NIH Grant NS093998

NIH Grant NS044375

Title: Functional tract tracing with intracortical microstimulation and intrinsic optical imaging can reveal distinct intracortical neural circuits within somatosensory cortex

Authors: *R. M. FRIEDMAN[1], M. M. CHERNOV[1], D. G. ZARAZA[1], A. W. ROE[1,2]
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Abstract: Electrical microstimulation has been used to modulate behavior, study the functional organization of the brain, and drive human brain-machine interfaces. However, how local and distant neural circuits are activated by electrical microstimulation is not well understood. We

previously demonstrated that intrinsic optical imaging (IOI) can reveal cortical activity produced by intracortical microstimulation (ICMS) in primate somatosensory cortex (SI) (Brock et al. 2013, J Neurophys) and known anatomical projections between somatomotor cortical areas (Stepniewska et al. 2011 PNAS; Kudyba et al. 2013 SFN Abstr #495.21). Here, we report on the patterns of activation in finer detail. Data were obtained from rhesus and squirrel monkey SI. Following IOI mapping of digit representation in response to vibrotactile stimulation of the finger pads, an electrode was placed tangentially to the surface of cortex (20-30 degrees) and advanced in superficial layers across the digit representation in 200-300 μm steps. Trains of electrical stimulation (bipolar, 0.4 ms pulse width, 250 Hz, 250 ms, 15-100 μA) were applied and optical images were acquired. We found that small advances in the electrode position within the same cortical finger pad cortical representation could evoke different patterns of activation. These patterns are consistent with anatomical tracer studies which show clustering of anatomical connections in areas 3b and 1 (Négyessy et al. 2013 J Comp Neurol; Ashaber et al. 2014 J Comp Neurol; Negyessy et al. 2015 SFN Abstr #515.09). In summary, patterns of cortical activity evoked by ICMS are consistent with the idea that distinct modality specific intracortical networks underlie tactile feature extraction in SI.

Disclosures: R.M. Friedman: None. **M.M. Chernov:** None. **D.G. Zaraza:** None. **A.W. Roe:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.01/DD25

Topic: D.04. Somatosensation: Touch

Title: Weight perception behavior of Japanese macaque monkeys

Authors: *M. TAOKA, S. HIHARA, T. KOIKE, A. IRIKI
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Abstract: Three Japanese macaque monkeys performed three weight discrimination experiments (Experiments 1,2, and 3), using objects that were different in weight but were the same in shape, size, color and texture.
Experiment 1; monkeys were trained to choose a lighter object between a pair of two (12g vs 188g for monkeys 1 and 2, and 21g vs 188g for monkey 3) with one hand. After 3-5 days, the correct choice ratios reached 95% for all three monkeys. Then, the heavier object (188g) was replaced with lighter objects (143g, 67g, etc.). All the monkeys chose the correct object in the first test session (> 10 trials) with correct choice ratios > 95% indicating that macaque monkeys are able to detect the weight difference with the hand.
Experiment 2; monkeys were tested with the same two-choice test using the other hand (naive

hand) without any training (untrained-hand test). All the monkeys showed nearly the same performance in the untrained-hand test as in the trained-hand test (correct choice ratios > 95%). This suggests that the brain center for weight judgment is shared for the two hands. In Experiments 1 and 2, the monkeys were always required to choose the same object as the lighter one (12g for the monkeys 1 and 2, and 21g for the monkey 3). There are two possible cognitive judgements to choose the correct object; lighter-heavier judgement or just choosing the same object in weight, which lead us to proceed to the next experiment (experiment 3).
Experiment 3; monkeys were trained to choose the lightest object among three objects. In the pre-test training sessions, various test-sets composed of three objects with different weights were prepared that always included a 21g object as the lightest one, so the monkeys were required to choose the 21g object in all test-sets. After correct choice ratios reached 95%, the test session started. Each test session was composed of 10 trials including one test-trial where the lightest object (21g) was replaced by a heavier one, but was still lightest among the three; for example, a session composed of 9 trials of 21g-83g-110g and one test-trial of 43g-83g-110g. All the monkeys almost always performed the task correctly (93%, 107 sessions) from the first session. In this experiment, the monkeys learned to choose the same object (21g) in the pre-test trainings but they chose the lightest one in the test trials.
These results demonstrate the establishment of lighter-heavier judgement without any specific training, further suggesting the importance of the generalized ability to detect relative differences in weight judgments.

Disclosures: **M. Taoka:** None. **S. Hihara:** None. **T. Koike:** None. **A. Iriki:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

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Topic: D.04. Somatosensation: Touch

Support: MIUR Grant PRIN2010-2011

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Title: Thalamic afferents of the macaque superior parietal areas PE and PEc

Authors: D. IMPIERI[1], L. PASSARELLI[1], S. BAKOLA[1,2,3], M. GAMBERINI[1], M. G. P. ROSA[2,3], *C. GALLETTI[1]
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Monash Univ., Clayton, Australia; [3]Australian Res. Council, Ctr. of Excellence for Integrative Brain Function, Monash Univ. Node, Clayton, Australia

Abstract: The dorsal surface of the superior parietal lobule in the macaque brain contains two cyto-architectonically defined areas, named PE and PEc. In area PE, the vast majority of cells responds to somatosensory stimulation, whereas area PEc contains visual, somatosensory, and bimodal cells. In area PE there is a rough topographically organized map of the body, whereas in area PEc the body representation is not topographically organized, and it is mainly focused on the limbs. The aim of this study was to describe the thalamo-cortical connections of these two parietal areas. To accomplish this, retrograde neuronal tracers were released into the cortex of six hemispheres of five male adult monkeys (*Macaca fascicularis*). Tracers were injected into the cortical thickness using a micro-syringe or placed as crystals on the exposed cortex based on visual inspection of the brain. Cyto- and myelo-architectural analysis of histological material established that in six cases tracers were delivered within the limits of area PE, and in three cases within those of area PEc. Areas PE and PEc showed a similar pattern of thalamic connections. In both cases, thalamo-cortical afferents mainly originated from Medial Pulvinar, Lateral Posterior, Ventral Posterior Lateral, and Ventral Lateral nuclei, with some differences in the strength of connections. While area PE showed a stronger input from the Medial Pulvinar and Ventral Posterior Lateral nuclei, area PEc displayed a more balanced input from the four thalamic nuclei. Minor afferents came from Ventral Anterior and Medial Dorsal nuclei for both the parietal areas, and from Central Medial/Parafascicular complex for area PE and from Central Lateral nucleus for area PEc. The Medial part of the Pulvinar nucleus is a multimodal, associative region with visual cells, that are not retinotopically organized. The Lateral Posterior nucleus is implicated in associative and somatosensory functions. In the somatotopically organized Ventral Parietal Lateral and Ventral Lateral nuclei, labelled neurons were mainly found in a region corresponding to the leg representation. All these findings corroborate the sensory-motor nature of areas PE and PEc, and particularly their involvement in the processes related to leg movements, including locomotion.

Disclosures: D. Impieri: None. **L. Passarelli:** None. **S. Bakola:** None. **M. Gamberini:** None. **M.G.P. Rosa:** None. **C. Galletti:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

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Topic: D.04. Somatosensation: Touch

Support: JSPS KAKENHI Grant 17H03549

Title: Neurons in the secondary somatosensory cortex and its surrounding opercular regions discriminating bodily awareness of the self from others

Authors: M. TAOKA[1], S. HIHARA[2], *A. IRIKI[2]
[1]RIKEN Brain Sci. Inst., Wako-Shi, Japan; [2]RIKEN Brain Sci. Inst., Wako-shi, Saitama, Japan

Abstract: Previous studies reported that monkey SII (secondary somatosensory cortex) neurons exhibit more complex somatosensory response properties than the primary somatosensory cortex (SI) [e.g., attentional effects on neural activity, bilateral integration from both hemibodies, and large receptive fields (RFs) covering multiple body parts], suggesting that SII is at higher level of information processing than SI. Although the involvement of SII in tactile object recognition (Hsiao 2008) and the sensorimotor integration for manipulating objects with the hand (Taoka et al. 2013) are suggested, the functional role of SII has not been fully clarified because the existence of complete somatic maps in SII as well as the bilateral and large RFs has not been explained. Recently, we found large RFs in SII covering almost the whole body (Taoka et al. 2016) suggesting the presence of other functional roles in SII. We also reported the visual inputs in SII (Hihara et al. 2015) indicating that SII, previously thought to be a unimodal somatic area, is a multisensory area. These two findings lead us to hypothesize that SII is related to self-body consciousness.
Initially, we trained a Japanese macaque monkey to recognize the mirror image of its whole body. Then, a total of 822 unit activities were recorded from the parietal operculum including SII of both hemispheres. We found many neurons that exhibited visual response (N=124, 15%), majority of them (N=96, 77%) having visual receptive fields (v-RFs) in peri-personal space of the monkey. Most of v-RFs were in the face exclusively (N=76), whereas 20 v-RFs were found around the forelimb, trunk and/or hindlimb which the monkey could recognize only through the self-image in the mirror set in front, demonstrating the “self mirror image recognition” at the neural level. Among remaining 28 visual neurons that responded to the presentation of moving object in the monkey’s visual field, six neurons responding to the moving object around the back of the monkey which the monkey could see only through the mirror. We found other types of neural activities that might be related to self vs others discrimination; e.g., those becoming active only when the monkey touched self-body (N=7), mostly the mouth or face (N=5) by own hands. Other five neurons were active only when the monkey touched the experimenter’s body. These neural responses discriminating self and others recorded from neurons in SII and surrounding opercular regions suggest the involvement of these cortical areas in the establishment of self-consciousness of the monkey.

Disclosures: M. Taoka: None. **S. Hihara:** None. **A. Iriki:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

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Program#/Poster#: 681.04/DD28

Topic: D.04. Somatosensation: Touch

Title: Human tactile perception of the smoothness of parametric 3D-printed textures

Authors: *C. TYMMS[1], D. ZORIN[2], E. P. GARDNER[3]
[1]Computer Sci., [2]New York Univ., New York, NY; [3]Dept Physiology/Neuroscience, New York Univ. Sch. of Med., New York, NY

Abstract: Roughness is one of the most important qualities in haptic perception. It is a major identifier for judgments of material composition, comfort and friction, and it is tied closely to manual dexterity. Many studies on roughness perception have been conducted using various types of stimuli: Braille dots, photo-etched dot arrays, gratings, and natural textures such as sandpapers and fabrics. However, a comprehensive examination of a variety of surface textures has not been conducted, largely due to the inability to create a wide range of finely controllable surfaces. In this work, we present a set of experiments using a novel type of controllable stimulus: textures created with parametric modeling and high-resolution 3D printing. We manufactured a set of textured square plates with raised texture elements ("textons") varying in element spacing (0.625 to 1.375 mm), arrangement (isotropic and anisotropic), and diameter (0.1 to 0.5 mm). Two-alternative forced choice protocols were used to investigate the contributions of these parameters to roughness perception. Results indicated that larger spatial periods produce higher estimations of roughness (with Weber fraction 0.19). In general, subjects with smaller D2 and D3 papillary ridge spacing are better able to accurately distinguish between textures. Results also show that anisotropic textures with regularly arranged textures are perceived smoother than isotropic textures of the same wavelength, and larger texton sizes produce higher smoothness estimates at each spatial period. These types of parametric stimuli are well-suited for studying tactile sensations, and can be used in further studies on tactile roughness and smoothness perception and in related neurophysiological applications.

Disclosures: C. Tymms: None. **D. Zorin:** None. **E.P. Gardner:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: D.04. Somatosensation: Touch

Support: NIH NCCIH Intramural

Title: Comparing effective responses to deep pressure and C-LTMR-optimized gentle touch

Authors: A. NECAISE[1], L. K. CASE[1], J. LILJENCRANTZ[1], *H. OLAUSSON[2], M. C. BUSHNELL[1]
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Abstract: Moderate and deep pressure touch are commonly utilized in massage therapy and have been linked to reductions in stress, depression, and pain. Yet there is no understanding of how pressure exerts these affective benefits. We propose that unmyelinated pressure-sensitive afferents identified in animals (e.g. Mense & Meyer, 1985) may exist in humans and underlie these effects. Such a mechanism would parallel the pleasantness of light stroking touch, which has been linked to the activation of C low-threshold mechanoreceptor (C-LTMR) fibers, unmyelinated sensory afferents that respond to slow gentle stroking of the skin and activate opioidergic brain regions including the insula and cingulate cortex (Gordon et al., 2013; Olausson et al., 2002). We conducted preparatory psychophysical studies to initiate this line of research. We designed a novel apparatus to administer mechanical pressure stimuli using a programmable compression sleeve. We utilized this apparatus to identify the most pleasant intensity, frequency, and location for pressure stimulation. We then compared the affective benefits of pressure to those of light stroking—an established affective touch paradigm. Participants received blocks of gentle stroking, moderate compression, and painful and non-painful heat and rated their intensity, pleasantness, wanting, liking, and mood on visual analog scales. Participants also rated qualitative touch descriptors on the Touch Perception Task (Guest et al., 2011) to further characterize their affective experience. This pressure paradigm generated significant ratings of pleasantness of a comparable magnitude to ratings of gentle stroking. Similar affective touch descriptors were endorsed for gentle brushing and moderate compression. Compression of the lower leg at a moderate compression frequency and moderate intensity was the preferred pressure stimulus. Ratings of stimulus pleasantness were correlated with mood and anxiety. These results suggest that deep pressure induces a pleasant affective response, even when delivered by a mechanical apparatus. Given its similar perceptual qualities (level of pleasantness ratings and touch descriptors), deep pressure touch might be conveyed by pathways similar to those involved in affective gentle stroking.

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Poster

681. Somatosensory System: Human and Non-Human Primates

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Topic: D.04. Somatosensation: Touch

Support: VR Grant K2013-62X-03548

Title: Brain responses to natural touch recorded with intracranial stereo-EEG

Authors: *E. J. ERIKSSON[1], D. KRÝSL[2], J. NILSSON[2], K. MALMGREN[3], B. RYDENHAG[3], J. WESSBERG[1]
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Abstract: In this study we aim to investigate the brain's responses to gentle touch in patients that undergo clinical intracranial stereo-encephalography (SEEG).
The perception of touch to hairy skin is mediated by slow conducting C-tactile (CT) afferents and fast conducting Aβ afferents. CTs have low mechanical thresholds, respond strongly to caress-like stimuli, and are believed to signal pleasantness of touch. Previous studies using functional magnetic resonance imaging have shown that CT afferents project to the insula but not to primary (S1) or secondary (S2) somatosensory cortices.
The local ethical committee approved this study. Data was obtained from 3 adult patients (1 female) with focal refractory epilepsy undergoing SEEG as part of their pre-surgical evaluation. The number of electrodes, number of contacts used and placement was strictly individualized based on the medical information given by the basic evaluation of the patient. Pre-surgical MRI volumes and CT-angiograms were used to plan the implantation and a post operative CT was obtained for 3D reconstruction of the electrode placements.
All patients had electrode implantation in the left hemisphere. SEEG was recorded during soft brush stroking on the dorsolateral aspect of the forearm. Patients were seated comfortably in a hospital bed and instructed to relax and focus on the touch sensations. A trained experimenter manually delivered the stimuli with a hand held soft brush. A minimum of 100 repetitions on both the contra- and ipsilateral forearm was carried out. The brushing velocity was CT-optimal, i.e. around 3 cm/s. A fiber-optic sensor was attached alongside the bristles of the brush, marking the timing of brush contact with the skin.
In one patient with electrodes implanted in S1 and primary motor cortex (M1), contralateral

gentle touch induced event-related beta de-synchronisation (ERD) and subsequent beta rebound in these areas. S1 ERD exhibited a broader frequency range (15-30 Hz) compared to M1 (15-20 Hz), whereas the frequency range of the beta rebound was more similar between the two areas (15-30 Hz). Furthermore there was a late onset (~1000 ms) 5-10 Hz event-related synchronisation (ERS) observed in the electrodes implanted in the left precuneus to bilateral touch stimulation that may reflect the integration of Aβ and CT signaling. Further analyses will be carried out to investigate the connectivity between precuneus, S1 and the insula in the patients where electrodes were implanted in those regions.

Disclosures: E.J. Eriksson: None. **D. Krýsl:** None. **J. Nilsson:** None. **K. Malmgren:** None. **B. Rydenhag:** None. **J. Wessberg:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

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Program#/Poster#: 681.07/DD31

Topic: H.02. Human Cognition and Behavior

Support: Rutgers University Research Foundation (BRK)

Title: Neural correlates of orgasm intensity: An fMRI study in men

Authors: *K. ALLEN[1,2], B. KOMISARUK[2]
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Abstract: Previous studies e.g., (J Sex Med 2011;8:2269; Hum Brain Map 2002;16:1) have identified multiple brain areas in men that are associated with arousal, intensity of arousal, and orgasm. However, those studies did not identify brain areas that may be related to the intensity of orgasm.
Using functional Magnetic Resonance Imaging (fMRI), we collected data while male participants self-stimulated to orgasm in a 3 Tesla, Siemens Trio scanner. Participants were asked to rate the intensity of orgasm on a scale of one to ten. After pre-processing with AFNI, we used a whole-brain analysis to identify areas whose activity correlated with the self-reported intensity of orgasm. During the first four seconds of orgasm, reported orgasm intensity correlated with activity levels in the left frontal medial orbital gyrus and the right anterior cingulate cortex. These areas have previously been implicated in the intensity of rewards e.g., (Biol Psychiat 2004; 55:594; Cerebral Cortex 2008;18:652) and which we found to be active during orgasm (SFN 2014;63.14). The correlation between level of fMRI activity and self-reported intensity of orgasm that we observed suggests a salient role for these regions in sexual satisfaction.
The last four seconds of orgasm did not correlate with activity in any areas of the brain,

indicating that the intensity of orgasm is identified early in orgasm, and declines as orgasm progresses.

Disclosures: K. Allen: None. **B. Komisaruk:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.08/DD32

Topic: D.04. Somatosensation: Touch

Support: ERC Parietalaction

Title: Spatiotemporal dynamics of action observation during and after touch events: A stereo EEG study

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Abstract: While the neural system that underlies action observation in the human brain is well studied, its neural dynamics is largely unknown due to the domination of fMRI studies in the field. Here, we investigated the spatiotemporal dynamics of action observation in a stereo EEG study. We recorded from 40 epileptic patients (5193 leads) implanted with intracerebral electrodes while they observed videos of three classes of actions: skin-displacing, manipulation, and interpersonal (each with four exemplars) taken from Ferri et al 2015. We marked a contact event in all the videos as the moment the actor touches the target of the action (own skin in skin-displacing, an object in manipulation, other's skin in interpersonal), and aligned the z-scored gamma (50-150 Hz) responses to this event. First, we identified the leads that were responsive after contact by the criterion that the area under curve after contact was greater than zero for any of the action classes ($p<0.05$). 43% of the leads (2256 leads) were responsive. Second, we performed a 3 (Action class) x 7 (Time bin of 100 ms) on the responses after contact on the responsive leads to identify that leads that showed action class or time specificity. 25% of the responsive leads (584 leads) showed the main effects of action class or time ($p<0.05$, corrected for multiple comparisons by FDR). Next, we characterized these leads based on their time course. First, using a home-made software, we detected the "contact" leads that responded only after the contact with an initial sharp rising response. These leads were concentrated in PFcm, PFop, OP1. When we removed the strict criterion and allowed the leads that had a rising component slightly before the contact, we additionally got responsive leads in a more distributed network of temporal, parietal, premotor, and cingulate cortex possibly reflecting the expectation of the contact event. Next, we further characterized the "contact" leads by examining their

response profile during the full course of the action exemplars. We identified two distinct types of responses: leads that responded phasically to contact events shortly for different types of target and leads that responded to contact events as well as the skin-displacing action following the contact till the end of the video. Finally, we also observed leads in the same region that did not have a phasic contact response but responded during the full course of the skin-displacing action after contact. These results highlight the importance of studying actions as temporally unfolding events using temporally resolved direct recordings to understand the spatiotemporal dynamics of action observation. Supported by ERC Parietalaction.

Disclosures: B.A. Urgen: None. **P. Avanzini:** None. **V. Pellicia:** None. **R. Mai:** None. **G. Lo Russo:** None. **G.A. Orban:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.09/DD33

Topic: F.08. Biological Rhythms and Sleep

Support: Brown Institute for Brain Science

Center for Neurorestoration and Neurotechnology, Providence VA Medical Center

Norman Prince Neuroscience Institute, Rhode Island Hospital

Title: Modulation of tactile detection with concurrent EEG-tACS

Authors: *D. D. SLIVA[1], C. BLACK[2], U. AGRAWAL[3], M. A. LADOW[4], J. F. SANTOYO[1], P. BOWARY[5], B. D. GREENBERG[5,6], C. I. MOORE[1], S. R. JONES[1,6]
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Abstract: The dynamics of rhythmic alpha-band activity (7-14 Hz) may reflect active processes engaged to diminish relay of signals from thalamus to neocortex, effectively gating sensory information. Prior work in our lab has shown that cued attention can modulate neocortical alpha oscillations in primary somatosensory cortex (SI), and that pre-stimulus alpha power in SI predicts tactile detection (Jones 2010). Furthermore, transcranial alternating current stimulation (tACS) may be capable of entraining endogenous oscillations in specific frequency bands (Zaehle et al. 2010). This study utilized concurrent EEG and tACS over SI while participants took part in a tactile detection task. Stimulation was applied at individuals' endogenous alpha frequency to assess whether augmenting ongoing rhythmic activity can reduce detection of difficult-to-perceive stimuli. Tactile detection rates were significantly reduced from baseline for

participants who received alpha, but not for participants who received sham, stimulation. Moreover, consistent with prior reports, alpha power tended to be higher on trials in which stimuli at perceptual threshold were not detected, compared to those in which stimuli were detected. However, we did not find evidence that tACS entrained alpha activity. Therefore, in our task, tACS appears to be perturbing normal dynamics in some other way to impact detection performance. This preliminary analysis supports the view that rhythmic alpha activity in SI is associated with perceptual performance, and provides proof of concept that modulation of tactile perception using non-invasive stimulation is plausible. Future work will further investigate potential neural mechanisms underlying this behavioral effect.

Disclosures: D.D. Sliva: None. **C. Black:** None. **U. Agrawal:** None. **M.A. Ladow:** None. **J.F. Santoyo:** None. **P. Bowary:** None. **B.D. Greenberg:** None. **C.I. Moore:** None. **S.R. Jones:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.10/DD34

Topic: D.04. Somatosensation: Touch

Title: The relationship between joint position sense and range of joint motion

Authors: *M. RADZIKOWSKI, H. TANABE, K. HAGIO, K. NAKAZAWA
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Abstract: INTRODUCTION: It has been known that discharge rate of joint receptor is increased at the limit of the range of joint angle in animal studies. If this can be applied to human joint position sense (JPS), proprioceptive acuity may be increased at the limit of the range of motion. Differences in JPS among individuals has been investigated at the same target angles irrespective of participants' range of joint motion, however, it could be possible that the acuity and its neural mechanism differ individually when participants are targeting a single joint angle. Thus, in this study, we investigated proprioceptive acuity using the JPS test with setting the target angle depended on the participants range of joint motions. The purpose of this study was to determine the differences in JPS relative to the individual range of joint motion.
METHOD: Healthy young subjects (N = 7) performed the ankle JPS test with an active reproduction test. We set 0% at the full dorsiflexion and 100% at the full plantar flexion, and calculated the target position (10% - 90%) for each subject. One session consists of three practices with visual feedback using a monitor indicating the target position, continued by a five time trials without visual feedback. Participants were in supine position or prone position, and each position had two start positions (rest and neutral). Participants performed the JPS test in randomized order. We obtained the ankle joint angle data from an electrogoniometer and surface

electromyographic (EMG) signal from the soleus, medial and lateral head of gastrocnemius, and tibialis anterior muscles. The EMG data was recorded while the subject holding the target position (for 1 sec.) and normalized with the maximum voluntary contraction.
Results and Discussion: The results showed that absolute errors (AE) from the target angle at 10% and 90% were significantly lower than 40%, 50%, 60% ($p < .05$), and there were no significant differences between conditions. This result was in line with the animal results showing the higher sensitivity of joint receptors at the limit of joint range of motion. It was found that when the activity of antagonist muscles increased, the AE tended to be decreased. Overall, our results indicated that the proprioceptive acuity is higher near the limit of range of joint motion and lower in the middle range of joint motion. Although the underlying neural mechanisms are not fully understood from the current results, it was suggested that not only joint receptor but proprioceptive signals from the antagonist also contribute to the observed higher acuity at the limit of joint motion range.

Disclosures: **M. Radzikowski:** None. **H. Tanabe:** None. **K. Hagio:** None. **K. Nakazawa:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.11/DD35

Topic: D.04. Somatosensation: Touch

Support: Grant-in-aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (15K16354)

Title: The effect of hand position in external space on the integration of bilateral tactile stimulation in the primary somatosensory cortex

Authors: ***N. OTSURU**[1], S. KOJIMA[1], S. MIYAGUCHI[1], R. SASAKI[1], S. TSUIKI[1], Y. INUKAI[1], K. SAITO[1], M. MASAKI[1], K. YAMASHIRO[1], H. SHIROZU[2], S. KAMEYAMA[2], H. ONISHI[1]
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Abstract: The primary somatosensory cortex contains a somatotopic representation of the body surfaces (Penfield and Boldrey, 1937). However, to precisely detect the stimuli location in space, we must realign tactile coordinates relative to an external frame of reference. A previous study reported that when tactile stimuli were presented to both hands, temporal order judgments were better when both hands were positioned far apart in external space (Shore et al., 2005). This indicated that the integration of bilateral tactile information in the brain is modulated by the

position of both hands in external space. However, the neural dynamics remains to be elucidated. In this study, we recorded cortical responses to tactile stimulation of the left index, right index, and both fingers using magnetoencephalography. Responses were investigated in hands-close and hands-far conditions in 12 volunteers. In the hands-close condition, index fingers were placed 1 cm apart, whereas in the hands-far condition, they were placed 30 cm apart. To elucidate the effects of hand position in external space on the integration of bilateral tactile information, we used the bilateral integration score (BIS) [(response of right index finger + response of left index finger) − response of both index fingers]. A higher BIS indicated a higher suppressive integration with stimulation of both index fingers. In the bilateral primary somatosensory cortex, BIS was lower in the hands-close condition than that in the hands-far condition. These results suggested that the integration of bilateral stimulation can be modulated by hand position in external space.

Disclosures: **N. Otsuru:** None. **S. Kojima:** None. **S. Miyaguchi:** None. **R. Sasaki:** None. **S. Tsuiki:** None. **Y. Inukai:** None. **K. Saito:** None. **M. Masaki:** None. **K. Yamashiro:** None. **H. Shirozu:** None. **S. Kameyama:** None. **H. Onishi:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.12/DD36

Topic: D.04. Somatosensation: Touch

Title: Memory-based M100 component in the somatosensory cortex: An MEG study

Authors: *K. YAMASHIRO[1], D. SATO[1], H. ONISHI[1], K. SUGAWARA[1], N. OTSURU[1], S. NAKAZAWA[1], Y. YAMAZAKI[1], H. SHIROZU[2], A. MARUYAMA[1]
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Abstract: A previous study showed that the ON-M100 and OFF-M100 somatosensory electrical stimulations elicited a very similar change-sensitive component, in terms of the temporal profile and the location and orientation of the source, suggesting common generation mechanisms. However, we did not record the change-sensitive component earlier than M100 using electrical stimulation. Conversely, Onishi et al. (2010) recorded very clear M50 responses using on and off stimulation generated by the application and removal of a constant mechanical pressure. In the present study, we recorded cortical activation in response to the onset and offset of tactile stimulations driven by a piezoelectric actuator using magnetoencephalography to clarify the physiological significance of the M50 and M100 somatosensory components in ten (7 males and 3 females) healthy subjects. Three inter-stimulus intervals (ISIs) (0.5, 1.5 and 3 s) were randomly presented for each event. The results showed that i) M50 and M100 somatosensory events

elicited a similar topography and temporal profile; ii) M50 and M100 components were estimated in the contralateral primary somatosensory cortex (cS1) and bilateral secondary somatosensory cortex (S2), respectively; iii) cS1 activity was independent of ISIs, whereas S2 activity as a function of the duration of the steady state preceding the change (ISI) was similar for both events, and it increased as a function of ISIs and iv) there was a significant positive correlation among the amplitudes of M100 between on and off responses across subjects. These results suggested that ON-M100 and OFF-M100 have similar generation mechanisms as well as a similar physiological significance with respect to the automatic memory-based detection of somatosensory changes. Conclusively, M50 and M100 reflect stimulus- and event-driven components that have a differential physiological significance in the somatosensory cortex.

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Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.13/EE1

Topic: D.04. Somatosensation: Touch

Support: NHMRC project grant 1067353

Title: A tactile motion perception task sensitive to slowed nerve conduction in peripheral neuropathy

Authors: *S. MCINTYRE[1], G. BERGSTRÖM[2], J. CAPPER[3], C. COUGHLIN[4], I. WOODS[4], F. HENSHAW[5], R. VICKERY[6], I. BIRZNIEKS[7], P. BREEN[5]
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Abstract: Peripheral neuropathy is associated with a decline in tactile sensation; typically measured as sensitivity to brief touch, or vibration applied to the skin. Evoked peripheral afferent activity, if relayed to the central nervous system, is sufficient to perform these simple tasks. Therefore task performance reflects mainly axonal loss caused by neuropathy. Neuropathy also causes increased temporal dispersion due to slowed conduction velocity. A more complex task affected by axonal conduction velocities may enable early detection of neuropathy and distinguishing different underlying causes. We developed an apparent motion device for use in clinical settings, in which neighbouring skin locations are successively tapped. Four tactors 20

mm apart tapped the skin on the plantar foot or lower leg. Participants judged the direction of motion, which requires them to correctly order the sequential touch events in space and time. Performance on this task is likely affected by the increased dispersion in conduction velocities associated with peripheral neuropathy. Data were collected from volunteers diagnosed with neuropathy (7 female, 8 male, aged 43 - 84) and healthy controls (8 female, 7 male, aged 53 - 87). An adaptive staircase procedure was used to determine direction discrimination performance, defined as the area under the curve (AUC), with larger values indicating slower speeds were needed to make direction judgments. On both sites tested, performance was significantly worse for the neuropathic group (foot = 130 (44), leg = 136 (39) mean (SD) AUC) than for the control group (foot = 96 (33), leg = 111 (38) mean (SD) AUC; foot: $t(52) = 3.2$, $p = 0.002$; leg: $t(50) = 2.3$, $p = 0.024$). These results indicate that the apparent motion direction judgment task has potential diagnostic value for peripheral neuropathy. It may enable early detection of neuropathy, distinguishing of different underlying causes, and characterising disease progression.

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Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.14/EE2

Topic: D.04. Somatosensation: Touch

Support: CIHR MOP-130269

Title: Cortical processing of irrelevant somatosensory information from the leg is altered by motor attention during motor planning after stroke

Authors: *S. PETERS[1], K. E. BROWN[2], T. C. HANDY[1], S. GARLAND[3], R. STAINES[4], L. A. BOYD[5]
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Abstract: Background: The ability to actively suppress, or gate, irrelevant sensory information is needed for safe and efficient walking in sensory-rich environments. Both gating and motor attention alter somatosensory evoked potentials (SEPs) in healthy people, and after a stroke. The aim of this study was to examine to the effect of motor attention on processing of irrelevant somatosensory information during planning of plantarflexion movements after stroke. **Methods:**

Individuals with chronic stroke (5f, 5m; 70.2 ± 9.6 yrs), older (5f, 4m; 71.9 ± 7.1 yrs), and younger healthy controls (6f, 7m; 27.8 ± 4.7) participated. Tibial nerve stimulation was delivered at 2Hz while electroencephalography (EEG) recorded SEPs over the Cz electrode. Three conditions were tested in both paretic/left and non-paretic/right legs: 1) *control*, where participants were asked to remember a random 5 digit number, 2) *Attend To* the stimulated limb, and 3) *Attend Away* from the stimulated limb. In conditions 2 and 3, vibration (80 Hz) was applied over the lateral ankle to cue voluntary plantarflexion movements of the stimulated (*Attend To*) or non-stimulated leg (*Attend Away*). **Analysis**: Peak-to-peak amplitude of the N50/P50/N70 components were averaged for stimuli delivered during motor planning for each condition; change scores were calculated between each attention condition and control. A 3-way mixed-model ANOVA was performed for each SEP component with factors of Group (stroke, older, younger), Leg (paretic/left, non-paretic/right) and Condition (*Attend To*, *Attend Away*). **Results:** There was a Condition x Group interaction effect for N40 amplitude ($p = 0.021$). Post hoc tests indicated that all group means in the *Attend To* condition were different from each other ($p \leq 0.038$), with the stroke group showing the smallest difference from control. For the *Attend Away* condition, older controls and individuals with stroke were not different ($p = 0.203$), but other group comparisons were different ($p \leq 0.044$). There were no significant differences for the P50. For the N70, a main effect of Condition was found with no interaction effect ($p = 0.020$), indicating that *Attend T*o showed greater levels of gating than *Attend Away* for all groups ($p = 0.020$). **Conclusions:** Though all groups show attention-related changes to irrelevant somatosensory information from the leg during motor planning, the stroke group demonstrated the least amount of gating of irrelevant somatosensory information during motor planning. If attention alters the somatosensory stimuli from a leg movement, then directing attention may affect safe community walking.

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Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.15/EE3

Topic: D.01. Sensory Disorders

Support: Marie Sklodowska-Curie grant agreement No 642961

Title: Visual deficits do not affect haptic space perception

Authors: *J. NELSON[1], I. A. KULING[1], M. GORI[2], A. POSTMA[3], E. BRENNER[1], J. B. J. SMEETS[1]

[1]Vrije Univ. Amsterdam, Amsterdam, Netherlands; [2]Inst. Italiano di Tecnologia, Genoa, Italy; [3]Univ. Utrecht, Utrecht, Netherlands

Abstract: Lack of vision affects some forms of spatial perception in blind individuals. Vision is often the best or only method to determine the size, position, and distance of objects and environmental features; blind and visually impaired people must resort to other means in order to accurately assess their surroundings. While some spatial skills are maintained or enhanced in absence of vision, others are compromised. Fewer deficits are observed in people who became blind later in life, who can be as proficient as blindfolded sighted people. Performance in various tabletop tasks such as spatial reorientation and complex shape recognition has previously been explored, and no differences have been found in performance between blind and blindfolded sighted people. Localization of one's own hand and simple length reproduction, however, have yet to be investigated. Our goal was to determine whether visual impairment affects the perception of positions and lengths in peripersonal space. We expected reduced visual experience to induce specific deformations in spatial perception, so we measured the haptically perceived location of one's own hand and the position-dependent reproduction of distance. To do so, we conducted a study in which 132 blindfolded participants with varying degrees of visual impairment used a pen to draw three lines of the same length as a reference object they had previously held in their dominant hand. The starting positions of these lines were determined by guiding participants' non-dominant hand to specified points under the table and asking them to place the pen where they thought their hand was. Two of the points lay along the body midline, one 15 cm from the edge of the table, and one 35 cm away, and the third point lay 15 cm from the edge of the table and 20 cm off the midline, on the same side of the body as their dominant hand. Participants drew a lateral line away from the midline from each of these starting points in a predetermined but random order. We found no effect of (onset age of) visual deficit on performance. All participants showed equal ability to match the starting position of the pen to the position of their non-dominant hand. Participants drew lines that were shorter than the length of the reference object, and they tended to draw slightly longer lines when starting from the more distant midline target. Furthermore, the angle of the line from the off-midline target differed from that of the lines from the midline targets in the clockwise direction. Our results indicate that visual deficits have no effect on the ability to determine the location of one's own unseen hand or reproduce lengths in peripersonal space.

Disclosures: J. Nelson: None. **I.A. Kuling:** None. **M. Gori:** None. **A. Postma:** None. **E. Brenner:** None. **J.B.J. Smeets:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.16/EE4

Topic: D.04. Somatosensation: Touch

Title: Frequency and duration effects in vibrotactile detection by the Pacinian psychophysical channel

Authors: *D. KILINÇ, B. GÜÇLÜ
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Abstract: Our previous work based on the fast adaptive tracking procedure showed that improvement of psychophysical thresholds at longer stimulus durations (i.e. temporal summation) was independent of vibrotactile frequency in the Pacinian (P) channel. In this study, we measured psychometric functions at six frequencies (100, 150, 250, 350, 500, and 750 Hz) and five durations (10, 30, 100, 300, and 1000 ms) by the method of constant stimuli. Ten human subjects (6F, 4M; ages: 25-30) participated in the experiment. Sinusoidal bursts (rise/fall time: 10 ms) of mechanical displacements were applied on the middle fingertips of the subjects by using a cylindrical contactor (radius: 2 mm) in a two-alternative forced-choice detection task. The vibrotactile stimuli were superimposed on a 0.5-mm static indentation. Six amplitude levels were used around the threshold estimate of each subject. The amplitudes were randomized and repeated for 40 trials at each frequency-duration condition. Additionally, the order of all conditions, which were tested in different blocks, were randomized across subjects and experimental sessions. To find the psychometric functions, the probabilities of correct detection were fitted by a sigmoidal curve as a function of amplitude by nonlinear regression at each condition. The R2 values for the fits were mostly high (average: 0.88). The midpoints (i.e. thresholds) and the slopes at the midpoints were obtained from the psychometric functions. After aligned rank transform, repeated measures ANOVA was used to study the effects of frequency, duration and the interaction between them. As expected from previous work, thresholds had the characteristic U-shape of the P channel as the frequency varied ($F(5,45) = 42.50$, $p<0.001$) and duration had a significant main effect on the thresholds ($F(4,36) = 60.34$, $p<0.001$). There was an approximately 8 dB threshold improvement as the duration increased from 10 to 1000 ms, and this temporal summation effect was about constant across frequencies, i.e. no interaction ($F(1,9) = 4.84$, $p = 0.055$). Interestingly, the psychometric slopes were also influenced by frequency, somewhat like an inverted U-shape ($F(5,45) = 29.64$, $p<0.001$). The slopes increased with increasing duration ($F(4,36) = 26.58$, $p<0.001$), except at 750 Hz (frequency × duration: $F(20,180) = 3.85$, $p<0.001$). The results confirm and extend the previous findings about temporal summation in the P channel. We are working to develop a population model for predicting the effects of frequency and duration on the psychometric functions.

Disclosures: D. Kilinç: None. **B. Güçlü:** None.

Poster

681. Somatosensory System: Human and Non-Human Primates

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 681.17/EE5

Topic: D.04. Somatosensation: Touch

Title: Using MVPA-analysis to investigate the influence of prior information on the perception of vibrotactile stimuli

Authors: *P. KASSRAIAN FARD, N. WENDEROTH
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Abstract: Bayesian inference has become a standard modeling framework applied to the sensory system that suggests perception can be biased by prior expectations. Currently, the extent to which prior information influences the neural response to vibrotactile stimuli is not well understood. Here we used Support Vector Machine (SVM) classification of functional magnetic resonance imaging (fMRI) data to investigate, first, how the brain encodes vibrotactile stimuli; and second, whether these representations are changed by prior information.
Four second epochs of vibrotactile stimulation were applied to the fingertips of human subjects. Prior to the fMRI experiment the perceptual threshold was determined for each subject individually using a staircase procedure. In the first experiment subjects received either subthreshold or suprathreshold stimuli. Classification was performed on features extracted from different somatosensory and control regions of interest (ROI), which were defined anatomically. In accordance with hierarchical models of the sensory system, which propose that sensory information is sent from thalamus to sensory cortices and is then relayed to higher order regions for further processing, decodability in different regions implies integration at different stages of sensory processing. Stimulation epochs were classified against rest using 10-fold crossvalidation and parameter optimization with a grid search. The main outcome parameter was classification accuracy. Preliminary analyses revealed that above-threshold vibrotactile stimulation of different digits can be classified with high accuracy ($> 75\%$, $p < 0.05$) in the contralateral postcentral gyrus (S1), and bilaterally in the secondary sensory cortex (S2). Moreover, we could distinguish between different stimulation intensities, even when all intensities were suprathreshold. Interestingly, differences in classification accuracy reflected proximity between stimulation intensities (although this relationship appears to be non-linear).
In the next step we will modulate the perception of near-threshold stimuli by providing prior information while keeping the physical characteristics of the stimulus constant. We will test whether prior information changes the classification accuracies of vibrotactile stimulus strength in primary or secondary somatosensory areas.

Disclosures: P. Kassraian Fard: None. **N. Wenderoth:** None.

Poster

682. Taste Coding

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 682.01/EE6

Topic: D.05. Olfaction and Taste

Support: Productos Medix

Fronteras de la Ciencia 63

Problemas Nacionales 464

Title: Encoding of sucrose palatability and its enhancement by auditory cues in the nucleus accumbens shell

Authors: *M. A. VILLAVICENCIO CAMARILLO[1], M. G. MORENO[1], S. S. SIMON[2], R. GUTIERREZ[1]
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Abstract: The over consumption of sucrose is one of the main culprits of obesity. In addition of its pleasant sweet taste, the consumption of sucrose is under the control of environmental cues that enhance its palatability. Nevertheless, it is not known the neuronal correlates of this multisensory integration in the nucleus accumbens shell (NAcSh). To answer these questions, we designed three variants of a brief-access test to measure palatability responses of water and sucrose in different cross-modal behavioral contexts, and recorded single-unit activity of NAcSh neurons. The Gustatory test measures palatability only using gustatory information, whereas the Start test adds an auditory Start cue and the Start/Stop test uses two auditory cues to signal when to start and stop licking in the Reward epoch (5 s duration). Our behavioral results indicate that both auditory cues enhanced sucrose palatability but in different ways: the Start test by accelerating water rejection, whereas the Start/Stop test by increasing the first bout duration and caloric intake of sucrose. Our electrophysiological results uncovered three NAcSh populations conveying information about sucrose. One whose firing rate correlated with oromotor-palatability responses, whereas a distinct population encoded sucrose sensory information by increasing or decreasing its firing rate as the concentrations of sucrose augmented. Another population increased its synchrony with licking. Finally, in an exclusive way, NAcSh neurons that were Inactive during licking also responded with a phasic activation to the auditory cues and thus they are well posit to perform a multisensory integration to guide feeding responses. In summary, here we uncovered how the NAcSh encodes sucrose palatability and concentrations, in different cross-modal behavioral contexts and found a new code implemented by NAcSh neurons based on its synchrony with licking. Importantly, we also showed that the NAcSh Lick-Inactive

neurons (putative medium spiny D1 neurons) integrate appetitive, palatability and auditory information in order to control feeding and to modulate the expression of sucrose palatability.

Disclosures: M.A. Villavicencio Camarillo: None. **M.G. Moreno:** None. **S.S. Simon:** None. **R. Gutierrez:** None.

Poster

682. Taste Coding

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 682.02/EE7

Topic: D.05. Olfaction and Taste

Support: Productos Medix

Problemas Nacionales 464

Fronteras de la Ciencia 63

Title: The representation of sweet taste intensity in the anterior/posterior insular cortex and orbitofrontal cortex in rats

Authors: *E. G. FONSECA DE LA CRUZ[1], F. ZEPEDA[2], S. A. SIMON[3], R. GUTIERREZ[4]
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Abstract: Sweet taste signals the presence of immediate energy sources. Similar to all taste qualities, its consumption is modulated in an intensity dependent manner. Yet it is not well understood how sweet taste intensity is represented in primary and secondary gustatory cortices in freely licking animals. To address this issue, we performed single unit recording in the anterior and posterior insular (aIC and pIC) and orbitofrontal cortex (OFC) while rats classified different concentrations of sucrose as either low or high intensity. First, rats were trained in a sucrose intensity discrimination task that consisted on five epochs indicated in parenthesis: In a central spout rats licked an empty sipper and starts a lick bout (Bout Start, BS) after 2-3 dry licks they received a (Cue) 15µl drop of 3%-low or 18%-high sucrose, subsequent dry licks continued until the Bout End (Bout End, BE); then rats moved to a lateral spout (i.e., the low or high lateral port) to initiate a lick bout (BSRew), if response was correct they were rewarded by 3 drops of water, which they consumed until last lick in lateral port (BERew). Once rats learned the task, classification sessions were introduced: 80% were training trials and 20% classification trials were rats received (0,3,4.75,7.5,11.75,18%) sucrose intensities and classified them as “low” or “high” (no reward delivery). We analyzed data in all 5 epochs. All brain regions recorded contains neurons that monitors all task epochs either with an inhibition, phasic or tonic

excitations or by firing in synchrony with licking. In pIC the proportion of licking coherent neuron was higher and these neurons continued oscillating during body movement epochs (BE and BERew). Lick-coherent neurons oscillated out of phase between pIC and OFC, and some of them increased/decreased their coherence after receiving cue. We also found that sucrose intensity discrimination information increases from Cue to BSRew epochs in both pIC and OFC. Indeed, neurons in pIC and OFC monotonically increased their firing rates in an intensity dependent manner and this activity correlated with behavioral choices. Interestingly, only OFC neurons increased their firing rate before leaving the central spout and sustain this activity during body movement to the lateral spout before receiving an impending reward. This activity nearly matched subjects' behavioral decisions. We are still recording in aIC. We conclude that single unit activity in both pIC and OFC discriminates between sucrose intensities. Nonetheless, OFC sucrose selective responses were better to maintain a sweet intensity representation which might be useful for decision making and guide behavior.

Disclosures: E.G. Fonseca de la Cruz: None. **F. Zepeda:** None. **S.A. Simon:** None. **R. Gutierrez:** 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.; Productos Medix, Problemas Nacionales 464, Fronteras de la Ciencia 63.

Poster

682. Taste Coding

Location: Halls A-C

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Topic: D.05. Olfaction and Taste

Support: SNSF Fellowship P300PA_161021

NIH NIDCD Grant R01-DC012543

NIH NIDCD Grant R01-DC015234

Title: Role of sensory and limbic thalamic nuclei in processing taste-related information

Authors: *R. VINCIS, K. CHEN, A. FONTANINI
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Abstract: The gustatory cortex (GC) is involved in the complex integration of sensory and reward-related information associated with the experience of eating. GC achieves this level of integration by processing multiple inputs from sensory and limbic areas. The thalamus is typically viewed as the source of bottom-up, sensory signals to GC. However, our knowledge about the involvement of the thalamus in taste is based solely on studies of the first order sensory

gustatory thalamus (VPMpc). Based on anatomical evidences, other higher order limbic thalamic nuclei normally devoted to multisensory and reward processing, such as the mediodorsal thalamus (MD) can potentially interact with the gustatory system. Here, by using anatomical, electrophysiological and behavioral techniques, we investigated the role of sensory and limbic thalamic in processing gustatory information in mice.
In a first set of animals we injected the retrograde tracer CTB-555 in GC in order to map the somata of thalamic neurons that send direct afferents to GC. We found that distinct groups of thalamic neurons located in the high order limbic mediodorsal (MD) and rhomboid/reuniens (henceforth called medioventral, MV) nuclei send direct and ipsilateral projections to the portion of GC that also receive inputs from the VPMpc. Next, we investigated whether neurons in the three thalamic nuclei process different variables associated with a gustatory experience. Mice were implanted with a linear array of 16 movable electrodes in one of the three thalamic nuclei and with a head-post for head restraint. Neural activity and licking behavior were recorded while mice were engaged in multiple behavioral tasks designed to investigate chemosensory processing, active sampling and cue-taste associations. We found that while all three thalamic nuclei have neurons that are strongly modulated in anticipation of licking, they also differ in the type of taste-related information they compute. VPMpc and MD carry information about taste identity, albeit with different tuning properties. MD and MV preferentially encode for taste-outcome specific expectancy.
Overall our results show a complex involvement of the thalamus in processing taste-related information. The presence of multiple thalamic inputs to GC demonstrates the pivotal role of both sensory and limbic thalamic nuclei in driving GC activity and its potential role in modulating taste-related behaviors.

Disclosures: **R. Vincis:** None. **K. Chen:** None. **A. Fontanini:** None.

Poster

682. Taste Coding

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Topic: D.05. Olfaction and Taste

Support: NIDCD R03-DC0143198

Basic Research Grant, University of Louisville School of Medicine

Title: Single-unit representation of flavor in gustatory cortex

Authors: *C. L. SAMUELSEN
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Abstract: The simultaneous activation of the taste and olfactory systems during food consumption results in the multimodal integration of taste and smell, necessary for the perception of flavor. The gustatory cortex (GC) is an area of chemosensory convergence and vital in processing this multisensory information. In a previous experiment, we showed that intraoral odors and palatable tastes evoke similar responses in GC bimodal neurons (those neurons responsive to both tastes and odors). Furthermore, a brief access task showed that animals sample palatable tastes and odors similarly, while avoiding non-palatable tastes (Samuelsen and Fontanini, 2017). The results of this experiment suggested that GC bimodal neurons might represent the hedonic properties of both types of chemosensory stimuli. To test this hypothesis, we first gave rats experience with two hedonically different flavors: a pleasant taste-odor pair (0.1M sucrose - 0.01% isoamyl acetate [S-IA]) and an unpleasant pair (0.2M citric acid - 0.01% benzaldehyde [CA-B]). Rat odor preferences were then confirmed with a two-bottle access test. After flavor experience, we recorded single-unit activity in the GC of behaving rats during the intraoral delivery of tastants, odorants, and flavors. Our preliminary results suggest that the intraoral delivery of odor evokes responses in GC bimodal neurons that are similar to that of the paired taste; i.e. evoked response to isoamyl acetate is more similarly to palatable tastes and benzaldehyde evoked responses are more similar to aversive taste stimuli. These data, in concert with unimodal responses to tastes and odors after flavor experience, suggest GC to be a pivotal node for processing the quality and hedonic properties of olfactory and gustatory information after flavor experience.

Disclosures: C.L. Samuelsen: None.

Poster

682. Taste Coding

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Topic: D.05. Olfaction and Taste

Support: Intramural Program of the NIMH; ZIA MH002588-26

Title: The neural basis of abnormal taste processing in autism spectrum disorders

Authors: *C. RIDDELL[1], J. AVERY[1], J. E. INGEHOLM[1], S. E. WOHLTJEN[2], M. A. COLLINS[1], S. MILLEVILLE[1], L. KENWORTHY[3], S. J. GOTTS[1], G. L. WALLACE[4], W. K. SIMMONS[5], A. MARTIN[1]
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Abstract: Abnormal or 'picky' eating habits, including food selectivity, food refusal, and insistence on sameness while eating, are common among those with Autism Spectrum Disorders (ASD). These behaviors likely result from atypical sensory processing, including a gustatory hypersensitivity, and often lead to both significant caregiver stress, as well as an increased risk for poor health outcomes (e.g., malnutrition). Despite the prevalence of atypical eating behaviors in ASD, very little is known about the neural mechanisms that underlie abnormal taste sensitivity in autism.

We recruited both young adult and adolescent males diagnosed with ASD (n=20), and neurotypical age and gender-matched controls (n=21) to undergo functional MRI while performing a variety of tasks that examine neural responses to food stimuli. Taste sensitivity was assessed behaviorally using the Adolescent and Adult Sensory Profile. During a gustatory mapping task, subjects received sweet and neutral tastants during fMRI scanning via an MRI-compatible tastant delivery system. In a separate imaging task, subjects viewed pictures of various appetizing foods as well as pictures of non-food objects. Subjects also underwent resting scans for the examination of intrinsic functional connectivity. We performed a series of analyses to identify group differences in response to the sight and taste of food, as well as to identify how taste sensitivity interacts with the neural response to food stimuli in ASD and neurotypical individuals.

We identified a network of brain regions that exhibited a significant interaction between diagnostic category and taste sensitivity, including the bilateral superior temporal sulcus (STS), the right ventral striatum, the left fusiform gyrus, and the dorsomedial prefrontal cortex. These regions have all been previously implicated in the neuropathology of ASD. Within these regions, ASD subjects with the greatest taste sensitivity exhibited the greatest response to sweet vs. neutral tastants. Importantly, these same regions exhibited a similar interaction effect within our food pictures task, indicating that the atypical response to food stimuli within these regions extends to both the sight and taste of food. Lastly, we identified that this interaction of group and taste sensitivity was also manifested in the resting-state functional connectivity between the bilateral STS and the bilateral dorsal mid-insula. This suggests that hypersensitivity to taste in ASD results from heightened connectivity between primary taste cortex in the mid-insula and higher-order sensory association cortices, leading to abnormal processing of food-related stimuli.

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Poster

682. Taste Coding

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Program#/Poster#: 682.06/EE11

Topic: D.05. Olfaction and Taste

Title: Taste associated with vision color in Japanese students

Authors: *S. NAGAHAMA
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Abstract: There may be many mechanisms about the influence of visual information on taste reception, and the complex interaction between two sensory modalities. The author reported that colors can influence a person's ability to distinguish threshold levels of basic tastes (Neuroscience 2016). Results of the threshold tests showed that red color had the effect of lowering the threshold of sweet taste, on the other hand blue color had the effect of raising the threshold of sweetness. In the case of salty taste, both red and blue color decreased the threshold of saltiness. Sour and bitter taste sensitivity were not affected by both colors. The author hypothesized that the effect of color on taste threshold is affected by cultural background and the environment. This study focused on the cross-modal correspondence between tastes and vision/colors. A total of 158 participants took part in this study (ranging from 20 to 22 years; 116 males and 42 females). The images of color patches were projected using a projector in the classroom. The images of color patches used 11 different colors, including black, blue, brown, green, gray, orange, pink, purple, red, white, and yellow. After they looked at a color patch, they chose the taste that they associated the color with, among 5 basic tastes (sweet, salty, sour, bitter and umami). Results of associations of colors with tastes showed that some colors were certainly more strongly associated with one taste than other tastes. The results revealed some cross-modal association between black with bitter, white/blue with salty, yellow with sour, pink with sweet and blown/red with umami. There wasn't much of differences between males and females. The above results of Japanese participants were similar to that had been reported for participants of many countries (Spence et al, 2014). Though lots of differences were accepted with Japan and the foreign countries by food culture and environment, it is suggested that Japanese and foreigners may be common in cross-modal correspondence between tastes and colors.

Disclosures: S. Nagahama: None.

Poster

682. Taste Coding

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Topic: D.05. Olfaction and Taste

Support: NIDCD DC006666

Title: The effects of amygdala input on taste-related activity in gustatory cortex

Authors: *J.-Y. LIN, N. MUKHERJEE, J. WACHUTKA, D. KATZ
Brandeis Univ., Waltham, MA

Abstract: Taste stimuli are richly laden with both chemical (taste identity, for instance sweet and salty) and behavioral/ingestion-decision related (palatability) information. Single neurons in the gustatory cortex (GC) evolve through a series of stereotypical firing 'epochs' in response to taste presentation - Following a brief, initial response to taste delivery, their firing conveys taste first identity information (Epoch 1: ~0.2-0.7s post-delivery) and then taste palatability (aka decision-related) information (Epoch 2: ~0.8s post-delivery). We hypothesize that the dynamic nature of GC taste responses is the result of the integration of temporally-restricted inputs from basolateral amygdala (BLA). Here we test this hypothesis by examining whether taste-related GC firing is altered by brief, targeted optogenetic perturbation of BLA-GC projections. We infected BLA of 4 adult female Long Evans rats with AAV-ArchT, and then implanted: 1) bilateral multi-electrode bundles with optical fibers ('optotrodes') in the GC; and 2) intra-oral cannula (IOC) for taste delivery. This preparation allows us to specifically silence BLA-GC projections while presenting a battery of taste stimuli that vary widely in their identity and palatability (0.1M NaCl, 0.3M Sucrose, 0.1M Citric Acid and 1mM Quinine-HCl). Here, we show that optogenetic inhibition of BLA-GC projections produces either an immediate or delayed suppression effect on GC taste responses. Regardless of the type of suppression, however, inhibiting BLA afferents has a larger impact on GC Epoch 2 than Epoch 1. This pattern of results is consistent with the hypothesis that, relative to other inputs, BLA primarily preferentially provides palatability information to GC. Future research will determine the impact of this brief, targeted optogenetic inactivation on taste-guided behavior, such as taste neophobia and conditioned taste aversion.

Disclosures: J. Lin: None. **N. Mukherjee:** None. **J. Wachutka:** None. **D. Katz:** None.

Poster

682. Taste Coding

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Topic: D.05. Olfaction and Taste

Support: HHMI International Student Research Fellowship 2014

NIH R01 DC006666-00

NIH R01 DC007703-06

Title: Taste-related cortical population dynamics are stochastic and behaviorally-relevant

Authors: *N. MUKHERJEE, J. WACHUTKA, J.-Y. LIN, D. B. KATZ
Brandeis Univ., Waltham, MA

Abstract: Dynamic processing of sensory stimuli by broadly distributed populations of neurons has been suggested to underlie the decision making processes that lead to the generation of appropriately timed behavioral responses. The mammalian gustatory (taste) system is particularly well suited for the study of the spatiotemporal neuronal dynamics that guides precisely timed behavior: consumption decisions are easily measured and shown to occur with a wide variability of latencies; Hidden Markov Model analyses reveal a similarly sudden, similarly variable emergence of coherent decision-related firing in simultaneously-recorded ensembles of gustatory cortical (GC) neurons, and demonstrate that the behavioral and neural variability are correlated on a trial-by-trial basis—such that the latter strongly predicts the former (Sadacca, Mukherjee, et al., 2016). Our current work uses brief and precisely-timed optogenetic perturbations to test the functional significance of this correlation. Our preliminary results demonstrate that: 1) GC population firing states are temporally dissociated, such that the disruption of an earlier state does not affect later states; and 2) perturbations timed late in the taste trial is most potent in disrupting the onset of orofacial behavior. Together, these data imply that GC activity is the outcome of cross-talk between several different brain regions, an "output" region that provides direct modulation of brainstem-generated taste-reactive orofacial movements as decision-related firing emerges. All in all, these results are allowing us to unravel the role of stochasticity in the processing of taste stimuli in GC ensembles and its behavioral significance in the context of brainstem controlled ingestion-egestion orofacial behavior.

Disclosures: N. Mukherjee: None. **J. Wachutka:** None. **J. Lin:** None. **D.B. Katz:** None.

Poster

682. Taste Coding

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Topic: D.05. Olfaction and Taste

Title: Cellular and synaptic properties of BLA and GC neurons relevant to CTA

Authors: *C. LIU[1], D. LEVITAN[1], V. VALAKH[1], D. B. KATZ[2], S. B. NELSON[1]
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Abstract: Conditioned taste aversion (CTA) is a form of classical conditioning in which a taste is associated with gastric malaise. The learning depends on activity and protein synthesis in gustatory cortex (GC) and basolateral amygdala (BLA), suggesting that changes in GC-BLA synaptic connections and/or in the cellular properties of neurons in these regions, may contribute to memory storage. Acute slice electrophysiology was used to identify candidate plastic changes

in mice. In BLA, excitatory drive onto parvalbumin+ (PV) fast-spiking interneurons was tested by measuring miniature excitatory postsynaptic currents (mEPSCs) and did not differ between CTA trained and taste-only control animals. Intrinsic excitability of BLA projection neurons was also unchanged after CTA. In GC, no change was found in the mEPSCs recorded in PV neurons. Since mEPSCs represent input from multiple sources, BLA specific changes might be diluted. To measure BLA input to GC directly, BLA projections were stimulated optogenetically. In initial experiments, two types of pyramidal neurons with different genetic labels, firing properties and projection destinations have been identified in layer 5 of GC. Two genetically distinct subsets of L2/3 neurons have also been identified, but they do not differ in firing properties. Input to different cell types will be analyzed separately since they may have different functions during CTA. In conclusion, the fact that intrinsic properties of BLA projecting neurons don't change with CTA, suggests changes are localized to synaptic connections between BLA and GC or within GC itself. Genetic dissection of GC circuits may improve our ability to measure and manipulate GC plasticity.

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Poster

682. Taste Coding

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Topic: D.05. Olfaction and Taste

Support: DA009815

Argentine Fulbright Commission and Argentine President's Cabinet: BEC.AR fellowship in Science and Technology 2014

Title: The profile of a range of neurochemicals in the nucleus accumbens shell differs for rewarding and aversive gustatory stimuli in rats

Authors: J. E. DOUTON[1], N. HORVATH[2], S. BALLARD[1], D. SUN[3], A. HAJNAL[5], *P. S. GRIGSON[4]
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Abstract: The dopaminergic projection from the ventral tegmental area to the striatum, in particular to the nucleus accumbens (NAc), has been suggested to be the major substrate mediating reward. As a key structure in this pathway, the NAc is widely interconnected with other important nuclei. It is expected, then, that behaviors that are modulated by this nucleus do

not depend solely on one neurochemical, but on an interplay amongst all inputs. Of course, one of the most basic questions related to the function of the NAc is how it responds to putatively rewarding and aversive stimuli. This study addresses this fundamental question by taking advantage of the fact that rats emit different stereotypic oromotor responses (taste reactivity) to tastants of different hedonic valence when they are infused directly into their mouth. Specifically, rats emit aversive taste reactivity behavior such as gapes to unpleasant taste stimuli like quinine and mouth movements, tongue protrusions, etc. to rewarding taste stimuli such as sucrose or saccharin. Here we collected microdialysis samples during the intraoral infusion of a sweet or a bitter solution and used a new method of benzoyl chloride derivatization with ultra performance liquid chromatography and tandem mass spectrometry that allows for the detection of up to 17 neurotransmitters and metabolites. Specifically, Sprague-Dawley rats were given 15 min access to either 0.03M quinine or 0.5M sucrose for 7 days. On the 8th day, eight microdialysis samples were collected from the right NAc shell. During the fifth sample, the taste solution was intraorally delivered while the oromotor response was recorded by video. Our results show that the intraoral infusion of quinine, but not sucrose, elicited aversive reactions. In addition, distinct neurochemical profiles were observed for the rewarding and aversive stimulus. Quinine elicited an increase in the concentration of DA, GABA, Ser, Glu, Gly and Hist, while sucrose also produced an increase in DA, but a decrease in GABA, Ser, Glu, Gly Hist.

Disclosures: **J.E. Douton:** None. **N. Horvath:** None. **S. Ballard:** None. **D. Sun:** None. **A. Hajnal:** None. **P.S. Grigson:** None.

Poster

682. Taste Coding

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Topic: D.05. Olfaction and Taste

Support: NIDCD Grant RO1 DC6013904

Title: Temporal coding of gustatory information in the NTS of lean and obese freely licking rats

Authors: *M. S. WEISS[1], A. HAJNAL[2], K. CZAJA[3], J. D. VICTOR[4], P. M. DI LORENZO[1]
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Abstract: Previous studies have shown that obesity changes both behavioral and brainstem electrophysiological responses to sweet tastes (e.g. Hajnal et al., *Am J Physiol Regul Integr Comp Physiol* 289:R1675-R1686, 2005). The aim of the present study was to study taste response profiles and taste-related information processing in neurons in the nucleus of the

solitary tract (NTS) of the diet-induced obese (DIO) rat. Following a minimum of 6 wks on a high fat diet (45% fat), obesity was verified via DXA body-composition scans (>18% body fat in obese rats vs. ~10% in lean rats). Rats were implanted with a chronic 16-ch drivable electrode bundle above the rostral NTS. Following recovery, rats were water deprived for ~22 hrs and placed in an operant chamber where they were allowed to lick freely. Tastants were presented in 5 consecutive lick trials interspersed with 5 licks of artificial saliva (AS) presented on a variable ratio 5 schedule. Tastants (dissolved in AS) were: NaCl (0.05 M), sucrose (0.1 M, 0.5 M), citric acid (0.016 M), caffeine (0.002 M), grape juice (0.1 M, 0.5 M), clam juice (0.025 M), heavy cream (25%), coffee (with 0.002 M caffeine), lemon juice (with 0.016 M citric acid) and AS. Results from 46 taste-responsive cells in DIO rats and 32 cells in lean rats show that the magnitude of taste responses that occur on a lick by lick basis to all stimuli are lower in obese rats ($F(1, 169) = 44.01$, $p < 0.001$). Taste-responsive neurons in obese rats were more narrowly tuned than those in lean rats ($X^2 = 5.072$, $p = 0.024$). To examine the contribution of the temporal characteristics of the response to coding taste quality, a family of metrics that quantifies the similarity of two spike trains in terms of spike count and spike timing was used (Victor & Purpura, *J Neurophysiol*, 76:1310-1326, 1996). These analyses indicate that for either 200 ms or 2 s of response, there was no difference in the amount of information about taste quality conveyed by the taste-evoked spike trains in obese (0.78 for 200 ms 0.97 bits for 2 s) vs. lean (1.0 for both 200 ms and 2 s) rats. These data suggest that taste stimuli drive NTS neurons more effectively in lean compared with obese rats. However, their ability to convey taste quality information remains intact.

Disclosures: M.S. Weiss: None. **A. Hajnal:** None. **K. Czaja:** None. **J.D. Victor:** None. **P.M. Di Lorenzo:** None.

Poster

682. Taste Coding

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Topic: D.05. Olfaction and Taste

Support: NIDCD Grant DC006914

Title: Optogenetic excitation of central amygdala terminals in the nucleus of the solitary tract targets responses to aversive tastes

Authors: *J. D. SAMMONS[1], C. E. BASS[2], P. M. DI LORENZO[1]
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Abstract: The gustatory portion of the nucleus of the solitary tract (NTS) receives information about taste directly from the periphery. It also receives centrifugal input from multiple cortical and subcortical brain structures, including the central amygdala (CeA). By integrating information from both peripheral and centrifugal input, the NTS can convey information about more than just taste quality, e.g. hedonic valence. Although no cortical or subcortical structure sends more projections to the NTS than the CeA, the functional relevance of the input from the CeA to the NTS remains poorly understood. Here, we used optogenetics to manipulate this input while recording from single cells in the NTS of awake, freely licking rats. First, an AAV2/10 viral construct encoding the gene for channelrhodopsin 2 (EF1α-ChR2-EYFP-AAV2/10) was infused into the CeA (-2.4 mm AP, ±4.0 mm ML, 7.8 DV with respect to bregma) of anesthetized rats bilaterally. After 2-4 weeks, rats were implanted with an optrode consisting of a fiber optic stub and an 8-microwire bundle of electrodes into the NTS. Following recovery, rats were presented with an array of taste stimuli under moderate water deprivation. Rats were given trials of 5 licks of a tastant (0.1 M NaCl, 0.1 M sucrose, 0.1/0.01 M MSG/IMP, 0.01 M citric acid, 0.001 M quinine, 0.1 M KCl, 0.1 M NH_4Cl, or artificial saliva) separated by 5 artificial saliva rinse licks presented on a VR5 schedule. In a random half of trials for each tastant, each lick of a taste stimulus triggered a 1 s train of laser light (25 Hz of 473 nm at 8-10 mW). Preliminary results show that excitation of CeA terminals in the NTS can selectively enhance responses to tastants with negative hedonic value, especially quinine. This suggests that the CeA may amplify the salience of tastants with negative hedonic value in the NTS. This is consistent with previous work showing that electrical stimulation of the CeA can increase aversive behaviors during tastant delivery (Riley & King, Chem. Senses 38: 705-717, 2013).

Disclosures: J.D. Sammons: None. **C.E. Bass:** None. **P.M. Di Lorenzo:** None.

Poster

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Topic: D.05. Olfaction and Taste

Support: NIH NIDCD R01 DC0114428

Title: Modality specific oral sensory disruption in chorda tympani and glossopharyngeal nerve responses after Hedgehog pathway inhibition in rat

Authors: A. KUMARI, Y. YOKOTA, R. M. BRADLEY, *C. MISTRETTA
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Abstract: Hedgehog (HH) is a major signaling pathway that regulates maintenance of taste papillae and taste buds (TB). HH regulation of taste organs and function has been studied by

analyzing effects of pathway blockade with the HH pathway inhibitor (HPI) drug sonidegib. Sonidegib blocks the HH pathway at the SMO signaling component and is used to treat patients with basal cell carcinoma originating from PTCH1 and SMO mutations that deregulate HH signaling. We have reported previously that TB in the fungiform papillae and responses from the chorda tympani nerve are eliminated in mice after administration of the HPI drug sonidegib for 16 days. However there are no studies in other rodent species to test effects of HH pathway inhibition by HPI drugs. Although the rat is an essential animal model for human physiology and disease, there is no demonstrated role for HH regulation in the rat taste system. We used oral gavage in rats aged 5 to 7 weeks to administer the HPI drug sonidegib or a vehicle control and then study taste organs, tongue epithelium, and effects on oral taste, touch and temperature sensation. We recorded whole nerve responses from the chorda tympani nerve (innervates TB in fungiform papillae, FP) or lingual branch of the glossopharyngeal nerve (innervates TB in circumvallate papilla, CV), and then collected tongues for analysis of FP, CV and TB morphology. In initial experiments, after 16-20 days of HPI sonidegib treatment, in chorda tympani or glossopharyngeal nerve, taste responses to stimulation of the respective tongue receptive field region with a broad panel of chemicals and range of concentrations were eliminated. TB in FP and CV were lost in parallel with the neurophysiological effects. However, in both nerves, responses to cold water and tactile stimuli were sustained, the latter transmitted by a set of large amplitude action potentials. With longer periods of HPI drug treatment, after 28 days of sonidegib for chorda tympani nerve recordings the responses to cold water also were eliminated but tactile responses were retained. However even after 35 days of sonidegib treatment for glossopharyngeal nerve recordings, responses to both cold water and tactile responses were maintained. Thus HH regulatory effects on lingual sensation are modality specific, and were observed in two taste organ systems, FP and CV, that derive from different embryonic tissues and have different chemical response profiles. We have found that lingual taste organs and taste, touch and temperature sensation from FP and CV systems are selectively altered by HH pathway inhibition in rat. The results also demonstrate efficacy of another rodent model for study of HH signaling in taste homeostasis.

Disclosures: **A. Kumari:** None. **Y. Yokota:** None. **R.M. Bradley:** None. **C. Mistretta:** None.

Poster

682. Taste Coding

Location: Halls A-C

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Program#/Poster#: 682.14/EE19

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH grant R01 DC00407

Title: Genetic deletion of sodium salt taste during development alters the dendritic architecture of gustatory relay neurons within the adult mouse nucleus of the solitary tract

Authors: *R. J. SKYBERG[1], D. L. HILL[2]
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Abstract: Neural activity plays a critical role in driving the development of many sensory circuits within the mammalian brain. By genetically manipulating specific taste transduction pathways our lab has been able to examine how neural activity impacts the functional and structural development of gustatory circuits. Removal of sodium salt taste by functionally deleting the gene for the alpha subunit of the epithelial sodium channel (αENaC) within taste bud cells throughout development led to a failure to "prune" gustatory afferent terminal fields within the nucleus of the solitary tract (NST). At adulthood, the chorda tympani (CT), glossopharyngeal (IX), and greater superficial petrosal (GSP) nerve terminal fields were 1.5X-2X larger in ENaC knockout mice than in controls; suggesting that ENaC-mediated neural activity is necessary for proper development of NST circuitry (Sun et al., 2017). The present study was designed to further explore the effects of eliminating ENaC-mediated sodium taste activity on the NST circuitry. Retrograde tracers were used to visualize the dendritic fields of NST relay cells -- the cells receiving input from gustatory afferent terminal fields -- in mice lacking ENaC activity and in littermate controls. Preliminary data suggests that the dendritic fields of these relay cells are also dependent upon neural activity to develop into a mature state. The dendritic arbors of relay cells in mice lacking ENaC activity throughout life were longer and less complex than in controls. Relay cell dendritic fields also were not oriented parallel to the solitary tract like is seen in control mice. Therefore, removal of neural activity throughout development has significant effects on both the presynaptic gustatory afferent terminal fields and the postsynaptic relay cell dendritic fields in the NST. These large anatomical changes likely impact physiological changes in how taste-related information is processed, thereby influencing sensory coding of taste, and behavioral consequences related to feeding and motivated behaviors.This work is supported by NIH grant R01 DC00407.

Disclosures: **R.J. Skyberg:** None. **D.L. Hill:** None.

Poster

683. Retina: Photoreceptors and Outer Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 683.01/EE20

Topic: D.07. Vision

Support: NIH Grant EY017836

NIH Grant EY014454

Title: Connectomic and optogenetic analyses of a circuit modulating the rod bipolar pathway

Authors: S. J. PARK[1], E. LIEBERMAN[2], J.-B. KE[2], N. RHO[2], P. GHORBANI[2], N. JUN[1], K. L. BRIGGMAN[3], J. B. DEMB[1], *J. H. SINGER[2]
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Abstract: Night vision in mammals depends on the rod bipolar (RB) cell-AII amacrine cell pathway. The RB-AII pathway receives input from rods and makes several well-established outputs to excitatory bipolar cells and to ganglion cells. But, critically, we lack an understanding of the inhibitory circuits that modulate RB-AII pathway function. Here, we identified the major inhibitory input to the AII by combining anatomical, genetic, and electrophysiological analyses in a three-step process. One, we reconstructed inhibitory synaptic inputs to AIIs in a volume of mouse retina imaged by scanning block face electron microscopy (SBEM) and found that virtually all of the inputs arose from a wide-field, multi-stratified amacrine cell (AC) with dendrites in both ON and OFF levels of the inner plexiform layer. Paradoxically, this AC received excitatory input solely from ON bipolar cells, in the OFF layers from en-passant axonal synapses and in the ON layers from more typical axon terminal synapses. Two, we evaluated published descriptions of reporter mouse lines to identify genetically-accessible ACs that had the anatomical characteristics of the cells reconstructed from SBEM images and selected the nNOS1 AC in the nNOS-creER mouse as a candidate input. And three, we used electrophysiological recordings and optogenetics-based circuit analysis of these cells to demonstrate that the nNOS1 AC provides GABAergic input to the AII. As well, the nNOS1 AC is a spiking neuron that exhibits a pure ON excitatory response, consistent with its identified bipolar cell input. Our study extends the classification of retinal neurons that receive ON input from en-passant axonal synapses made by ON bipolar cells in the OFF strata of the IPL to three: the nNOS1 AC joins the dopaminergic AC and the intrinsically-photosensitive ganglion cells in this category (citations). We conclude that the nNOS1-AC is the source of AII surround inhibition. More generally, our study demonstrates the utility of targeted, small-scale “connectomic” analysis for identification of novel neural circuits.

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Poster

683. Retina: Photoreceptors and Outer Circuits

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Program#/Poster#: 683.02/EE21

Topic: D.07. Vision

Support: FP7-PEOPLE-212-ITN 316832 `OLIMPIA'

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Istituto Italiano di Tecnologia pre-startup project

Title: A fully organic retinal prosthesis restores vision in a rat model of degenerative blindness

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Abstract: The degeneration of photoreceptors in the retina is one of the major causes of adult blindness in humans. Unfortunately, no effective clinical treatments exist for the majority of retinal degenerative disorders. In this work we report on the fabrication and functional validation of a fully organic prosthesis for long-term in vivo subretinal implantation in the eye of Royal College of Surgeons rats, a widely recognized model of retinitis pigmentosa. Electrophysiological and behavioural analyses revealed a prosthesis-dependent recovery of light sensitivity and visual acuity that persists up to 6-10 months after surgery. The rescue of the visual function was accompanied by an increase in the basal metabolic activity of the primary visual cortex, as demonstrated by positron emission tomography imaging. Our results highlight the possibility of developing a new generation of fully organic, highly biocompatible and functionally autonomous photovoltaic prostheses for subretinal implants to treat degenerative blindness.

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Poster

683. Retina: Photoreceptors and Outer Circuits

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Program#/Poster#: 683.03/EE22

Topic: D.07. Vision

Support: NSERC Discovery Accelerator Grant

Title: UV cone photoreceptors and putative molecular mechanisms of light-dependent magnetoreception

Authors: *S. D. BALAY[1], W. T. ALLISON[1,2]
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Abstract: Objective: The Earth's magnetic field serves as a navigational cue for a diverse range of organisms. This sensory information is used for animal homing, predator avoidance, prey capture, long distance migrations and more. Until recently, the literature has been dominated by behavioural evidence for magnetoreception, while the underlying mechanism for this phenomenon remains to be debated. Light-sensitive proteins called Cryptochromes (*cry*) are putative molecular candidates due to their biophysical properties: magnetic fields can alter their chemical products, they are activated by short wavelength light and are associated with retinal UV cone (*sws1*) photoreceptors in birds and the homologous blue cones in some mammals. Although *sws1* cones have been suggested to be crucial for magnetoreception, their role in *cry* expression has yet to be tested in any animal model. We sought to test if a specific *cry* isoform was expressed in retinal cone photoreceptor subtypes in zebrafish. **We hypothesized that *cry* is exclusively associated with *sws1* cones.** Loss of *sws1* cones was predicted to result in decreased expression of *cry*.
Methods: Using pharmacogenetic nitroreductase (NTR) mediated cell ablation via transgenic zebrafish, UV (*sws1*) or Blue (*sws2*) cone subtypes were selectively removed from zebrafish retina. Fluorescent in situ hybridization and RT-qPCR were used to visualize and quantify *cry* and *sws* gene expression.
Results: Zebrafish UV-cones express a *cry* isoform that appears to be non-circadian. This *cry* expression dramatically decreased by 62%±7% [$F(3, 20)= 4.90$, $p= 0.012$] when UV cones were ablated but not when blue cones were ablated [$F(3, 20)= 4.90$, $p= 0.90$] suggesting UV cone presence is required for robust *cry* expression. This study serves as the first experimental evidence that 1) cone photoreceptors are required for *cry* expression, 2) *cry* is co-localized in UV cones photoreceptors and 3) both may play a role in fish magnetoreception.

Conclusions: Zebrafish represent an excellent model for studying the proximate mechanisms of visually mediated behaviors, but have been under used in magnetoreception studies. Our lab has engineered a zebrafish line where cones can be selectively ablated from the retina, without disrupting other cells. This provides a unique opportunity to study the role of cone photoreceptors in *cry* expression and the mechanisms governing magnetoreception. Additional to our molecular work, *cry* mutants and novel behavioral paradigms are currently being designed to test the role of UV cones in zebrafish magnetoreceptive behavior.

Disclosures: S.D. Balay: None. **W.T. Allison:** None.

Poster

683. Retina: Photoreceptors and Outer Circuits

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Support: JSPS grant-in-Aid for Scientific Research

the Cooperative Research project program of the Medical Institute of Bioregulation, Kyushu University

Title: Retinal light damage in Ogg1 and Mouthy knockout mice

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Abstract: PURPOSE. To evaluate the roles of MutY homolog (MUTYH) and 8-oxoguanine DNA glycosylase (OGG1), base excision repair enzymes, in murine retinas subjected to oxidative stress.
METHODS. The left eyes of *Mutyh*- and *Ogg1*-knockout (KO) mice and C57BL/6J mice (wild-type) were exposed to light in the ultraviolet and visible region (center wavelength: 376 nm, bandwidth: 39 nm) from a xenon lamp light source with retinal radiant exposure of 75 J/cm^2. The unexposed right eyes served as controls. Seven days later, we recorded flash electroretinograms (ERGs) and measured the thickness of the outer nuclear layer (ONL). To confirm oxidative stress-induced DNA damage, we observed the accumulation of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG). Transmission electron microscopy showed retinal ultrastructural changes 1 and 3 days after exposure.
RESULTS. Light-induced retinal damage was suppressed partly in *Mutyh*-KO mice and not in *Ogg1*- KO mice. The ERG a- and b-wave amplitudes were decreased, and loss of the ONL was suppressed significantly in the *Mutyh*-KO mice retinas compared with wild-type mice. 8-oxo-dG expression in light-exposed retinas was suppressed compared with wild-type and *Ogg1*-KO

mice.
CONCLUSION. In *Mutyh*-KO mice, the lack of MUTYH partly suppressed the retinal damage induced by intense light exposure. Regulation of MUTYH expression or function might prevent retinal degenerative disease involved in oxidative stress.

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Poster

683. Retina: Photoreceptors and Outer Circuits

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PolyU grants: GSB44

Henry G Leong Endowment Professorship Fund

Title: The effect of spectral input on eye growth in young chicks

Authors: *K. CHUN[1], D. WANG[2], T. LAM[1], Q. LIU[3], C. TO[1]
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Abstract: Objective. To investigate the effect of different spectral compositions on the eye growth in young chicks. **Methods.** Four groups of young chicks aged 4 days (n = 8 in each group) were raised in four different lighting conditions; white light (W), combination of white and red (WR; 50:50), combination of white and blue (WB; 1:1 ratio) and combination of white, red and blue (WRB, 1:1:1) for 14 days in a 12/12-hour light/ dark diurnal cycle. Eye growth was monitored in terms of refractive errors and ocular parameters at the beginning (D0), 4 days (D4), 7 days (D7), 10 days (D10) and 14 days (D14) of exposure to specific lighting conditions. **Results.** In chicks under WB condition, a significant shortening of vitreous chamber depth (VCD) was found (-0.33 ± 0.07 mm) while the VCD of chicks under other lighting conditions increased after 4 days of exposure. A greater elongation of VCD was found in chicks under WRB condition as compare with those in W group at day 4 (WRB vs. W; 0.16 ± 0.06 mm vs. 0.07 ± 0.04 mm, $p < 0.01$, post hoc test, one-way ANOVA). After longer period of exposure, VCD of chicks in WB conditions increased but still in a smaller extent compared with other chicks at day 7, day 10 and day 14. The increase in VCD of chicks raised in WB was significantly smaller than other groups ($p < 0.001$). At day 14, chicks raised in WR had longer VCD compared to other groups (mean VCD at day 14; W vs. WB vs. WR vs. WRB; 5.98 ± 0.20

mm vs. 5.91 ± 0.16 mm vs. 6.26 ± 0.16 mm vs. 6.17 ± 0.26 mm). Chicks in WR conditions were relatively more myopic than those raised in white lighting alone at day 4 (mean change; WR vs. W; -2.19 ± 0.58 D vs. -1.19 ± 0.59 D, $p < 0.05$). At day 14, the chicks under WR were the least hyperopic while the chicks raised under WRB were the most hyperopic (mean spherical equivalent; W vs. WR vs. WB vs. WRB; +3.47 ± 0.36 D vs. +3.22 ± 0.47 D vs. +3.59 ± 0.23 D vs. 3.66 ± 0.52 D). However, the choroid did not demonstrate significant changes after the exposure. **Conclusion.** Spectral compositions of ambient lighting can significant affect eye growth in chicks. In a white light background, the addition of long-wavelength (red) light increased eye growth while short-wavelength light retarded it. The data suggested that chromaticity of the light and respective cone responses may contribute to eye growth in chicks. The white light background acts to help position the relative planes of focus of different wavelengths of light. This in turn enables differential activation of respective retinal cones and their responses to signal eye growth. Chromaticity may be an important optical cue to be decoded by the retina during eye growth.

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Poster

683. Retina: Photoreceptors and Outer Circuits

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Title: Synergistic signaling by light and acetylcholine in mouse iris sphincter muscle

Authors: *Q. WANG[1,2], W. W. S. YUE[1], Z. JIANG[1], T. XUE[3], S. H. KANG[1], D. E. BERGLES[1], K. MIKOSHIBA[4], S. OFFERMANNS[5], K.-W. YAU[1]
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Abstract: ***Introduction:*** The size of the pupil is determined by an antagonism between the circumferential sphincter muscle and the radial dilator muscle in the iris. Upon monocular illumination, the pupils in both eyes constrict to a broadly similar extent because of the bilateral reflex pathways through the brain. Despite this widely-accepted picture, the isolated iris

sphincter muscle of nocturnal and crepuscular sub-primates is now known to be capable of light-induced contraction. In mouse, this “intrinsic” pupillary light reflex (PLR) requires the visual pigment, melanopsin, originally found in intrinsically-photosensitive retinal ganglion cells (ipRGCs). However, melanopsin’s presence and effector pathway locally in the iris remain uncertain. In this study, we provide evidence based on pharmacological, genetic-labeling, and tissue-specific gene-knockout experiments to support that the local light signal causing iris-sphincter-muscle contraction indeed originates from melanopsin in the muscle itself. ***Methods:*** The effect of pharmacological inhibition of cholinergic synaptic transmission on the local pupillary light reflex was examined by comparing the light-induced contraction of the isolated mouse iris sphincter muscle in the absence or presence of atropine or TTX. Functional presence of melanopsin in the iris was examining by tissue-specific deletion of melanopsin in smooth muscle. Phototransduction cascade of the iris sphincter muscle cells was investigated using mouse lines lacking one or more candidate genes. ***Results:*** We showed that the muscarinic receptor antagonist, atropine, eliminated the effect of acetylcholine (ACh), but not of light, on isolated mouse iris sphincter muscle. Conversely, selective genetic deletion of melanopsin in smooth muscle mostly removed the light-induced, but not the ACh-triggered, increase in isolated iris sphincter muscle’s tension, and largely suppressed the local PLR *in vivo*. We found melanopsin expression in a small subset of mouse iris sphincter muscle cells, with the light-induced contractile signal apparently spreading through gap junctions into neighboring muscle cells. Light and ACh share a common signaling pathway in iris sphincter muscle. ***Conclusion:*** In summary, our experiments have provided details of a photosignaling process in the eye occurring entirely outside the retina, as well as its integration with autonomic neural control. Thus, mouse iris sphincter muscle cells are *bona fide*, albeit unconventional, photoreceptors.

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Poster

683. Retina: Photoreceptors and Outer Circuits

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Title: Protective effects of zinc and cAMP against A2E-induced toxicity in ARPE19 cells: Possible involvement of lysosomal acidification

Authors: *J. CHOI[1], B.-R. SEO[1], J.-Y. KOH[1,2], Y. YOON[3]
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Abstract: Dry age-related macular degeneration (AMD) is characterized by the accumulation of drusen and degeneration of photoreceptor cells and retinal pigment epithelial (RPE) cells in and around the macula. It has been proposed that phagocytic and lysosomal dysfunctions in RPE cells, which hinder the degradation of shed photoreceptor membranes, contribute to these pathological changes. According to our previous studies, raising intracellular zinc levels can restore lysosomal acidification in cases of arrested autophagy. Increasing intracellular and lysosomal zinc levels with a zinc ionophore clioquinol was highly effective in restoring lysosomal pH and degradation in chloroquine-induced arrest in autophagy. In addition, several studies have shown that raising cAMP levels are also effective in restoring lysosomal acidity and degradative function. With these findings as a backdrop, in the present study, we examined the effects of zinc and cAMP on lysosomal alkalization and dysfunction in a cell culture model of AMD. To induce lysosomal dysfunction in a human RPE cell line (ARPE19), we used A2E (lipofuscin derivative) and chloroquine (lysosomal alkalizing drug). Twenty four hours after the treatment with A2E, ARPE19 cells exhibited autofluorescence throughout the cell body, and eventually underwent cell death. On the other hand, as previously reported, chloroquine treatment induced vacuolar changes, lysosomal dysfunction, and cell death. Addition of zinc or dibutyryl cAMP reduced cell death in both cases. Moreover, zinc or dibutyryl cAMP decreased A2E autofluorescence in A2E-treated ARPE19 cells. In addition, we are currently examining the effects of zinc and cAMP on lysosomal parameters in A2E-treated ARPE19 cells. Present results support the possibility that adequate levels of zinc or cAMP may help overcome the cytotoxic effects of A2E or lysosomal alkalinizing agents, both of which may contribute to the pathogenesis of AMD.

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Poster

683. Retina: Photoreceptors and Outer Circuits

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Program#/Poster#: 683.08/EE27

Topic: D.07. Vision

Title: A psychophysical test of photophobia for blue and red light stimuli under binocular and monocular viewing conditions

Authors: M. ZIVCEVSKA[1], S. LEI[3], A. BLAKEMAN[3], *H. C. GOLTZ[5,2], A. M. WONG[4,2]
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Abstract: Objective: Photophobia is a light hypersensitivity phenomenon defined by light-evoked painful sensations. Photophobia is thought to be mediated by the melanopsin-containing intrinsically photosensitive retinal ganglion cell (ipRCG) light-irradiance pathway, which is selectively sensitive to blue light. We have previously shown that the melanopsin response is a function of the retinal area stimulated. We developed a psychophysical test for photophobia and hypothesized that participants will be more sensitive to blue light than red light stimulation. Since binocular viewing stimulates greater retinal area, we also hypothesized that a binocular viewing condition will induce more discomfort than monocular viewing. **Methods:** Eleven visually-normal participants (5 females; mean age 25 years; range 22-31 years) were recruited. Participants received dilating drops (2.5% phenylephrine) prior to the experiment to maintain consistent pupil size and thus light exposure. Full-field stimulation using a Ganzfeld system presented 7 randomized intensities (1 s each) of either red (2, 25, 50, 75, 100, 200, 400 cd/m^2) or blue (2, 10, 20, 40, 60, 80, 100 cd/m^2) light, 20 times for each intensity, in four 70 trial blocks. Constant white-light stimuli (3 cd/m^2, 4 s duration) were interspersed between the chromatic trials. Participants rated the light as either “uncomfortably bright” or “not uncomfortably bright”. The experiment was done binocularly and monocularly in separate sessions, and the color/viewing sequence order was randomized across participants. The proportion of “uncomfortable” responses was used to generate a psychometric function and the 50% discomfort thresholds were calculated individually. **Results:** Light sensitivity was highest under blue light stimulation compared to red light stimulation, both during binocular ($t_{(10)}$=-3.55, p=0.005) and monocular viewing ($t_{(10)}$=-3.14, p=0.01). There was also a significant difference in sensitivity between viewing conditions (monocular vs. binocular) for blue light (p=0.004), but not for red light stimulation (p=0.21). On average, binocular viewing decreased discomfort thresholds (more discomfort) by 56% for blue light, while only 10% for red light. **Conclusion:** Melanopsin-activating blue light induces photophobia at lower thresholds compared to red light. Additionally, photophobia thresholds are lower in binocular viewing conditions for blue light only, suggesting that the perceptual experience of photophobia is integrative in nature. Collectively, this evidence supports the idea that photophobia is an ipRGC-mediated phenomenon.

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Poster

683. Retina: Photoreceptors and Outer Circuits

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Topic: D.07. Vision

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Title: Identification and characterization of novel, conserved cone photoreceptor enriched factors

Authors: *A. SMITH[1,2], B. N. KENNEDY[2], A. SWAROOP[1]
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Abstract: The inability of the retina to detect and/or transmit light-triggered signals is largely responsible for incurable blinding conditions such as age-related macular degeneration, and cone-rod dystrophy, due to dysfunction or death of photoreceptor cells. There remains a lack of understanding of genes involved in cone development, function and survival, hinting at the existence of cone specific or cone sensitive processes.
This research aimed to identify novel factors expressed in cone photoreceptors in zebrafish and mouse, and in the macula of humans, using sequencing technologies. 27 novel, evolutionarily conserved, cone-enriched genes were identified in zebrafish and mice, using microarray, and RNAseq analysis, respectively.
These factors were confirmed to be conserved in human, and enriched in the retina. FISH revealed that the gene clul1 was specifically expressed in the cone photoreceptors of adult, and developing larval zebrafish. Molecular characterization of clul1 in zebrafish and primate retina has elucidated its localization and expression pattern.
Conclusively, novel conserved cone photoreceptor enriched factors have been identified, and *in situ* hybridization and immunofluorescence have been employed to elucidated their expression patterns and subcellular localization. Functional investigation of this gene using CRISPR-Cas9 is now leading to insights into its role in visual function, and its role as a cone photoreceptor enriched factor.

Disclosures: **A. Smith:** None. **B.N. Kennedy:** None. **A. Swaroop:** None.

Poster

683. Retina: Photoreceptors and Outer Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: D.07. Vision

Support: NIH Intramural Program EY000450

Title: Rod photoreceptor morphogenesis: Role of Snta1 for form and function

Authors: *D. T. WHITAKER[1,2], H. FANN[1], P. HARGROVE[1], A. ALSUFYANI[1], M. J. BROOKS[1], S.-Y. KIM[1], A. SWAROOP[1]
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Abstract: Structure and function are intimately connected within the nervous system. Neurons, from the brain to retina to spinal cord, have a diverse array of cellular morphologies that are unique and specific among the different functional populations. While much work has been done to uncover the exact physiological reasons why a cell or cell class has its defined shape, we are still more in the dark on the genetic factors that can help establish this structure. Using two closely related functional cell types, the light sensing rod and cone photoreceptors, that have similar but distinct morphologies, we sought to investigate those genes that could be playing a role in defining the morphological differences between the two. To accomplish our goal, we first characterized rod and cone (and cone-like) synaptic terminal structure. Then, we looked at the transcriptional landscape of developing rod and cone-like photoreceptors (similar to wild type S-cones) along with transcription factor binding profiles of key regulators of photoreceptor fate to identify a more workable list of candidates, 720 in total. From this, we selected and knocked down approximately 10% of these genes through *in vivo* electroporation of shRNAs and a rod-specific fluorescent reporter and assayed individual cells through quantitative analysis of the photoreceptor pre-synaptic terminal structure, specifically the depth within the connective layer between photoreceptors and interneurons and the size of the terminals. From these data, we have currently found 15 genes whereby knockdown in rod photoreceptors resulted in differential morphological features that are more similar to the cone than to the native rod. Confidence in these data is increased through knockdowns of the same genes with different shRNAs as well as rescue of some phenotypes. For one of our top targets, Snta1, we obtained the knockout mouse line. In this mutant, we see no gross alterations in retinal lamination or phototransduction, but we do see a large increase in the transmission of signal from rod photoreceptors to rod bipolar cells. This is exciting because it is the first example of such a result that we could find in the literature. These data show a direct correlation between neuron structure and function.

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Poster

683. Retina: Photoreceptors and Outer Circuits

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Topic: D.07. Vision

Support: UNMC Ophthalmology Start-up Funds

Title: Features of cone bipolar cell synaptic transmission onto retinal ganglion cells

Authors: *M. J. VAN HOOK
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Abstract: In the retina, approximately 12 classes of cone bipolar cells (CBCs) serve as intermediaries carrying rod- and cone-driven visual signals to retinal ganglion cells (RGCs). Despite CBCs' key roles in vision, most studies of mammalian bipolar cell synaptic function have relied on rod bipolar cells (RBCs), a specialized bipolar cell population specialized for dim light conditions. Thus, the basic properties of CBC synaptic transmission onto RGCs are unknown. The goal of this study is to characterize the Ca^{2+}-dependence, Ca^{2+} domain coupling, and short-term plasticity of CBC synapses onto RGCs. Whole-cell recordings were obtained from On- and Off- alpha-RGCs in flat-mounted mouse retinas and RGC identity confirmed with dye filling. CBC synaptic inputs were stimulated with current pulses delivered from an extracellular electrode positioned near bipolar cell somata. Extracellular [Ca^{2+}] was varied to assess the cooperativity of the CBC exocytotic Ca^{2+} sensor, while the L-type channel blocker nifedipine was applied to test for nano- vs micro-domain control of exocytosis. Paired pulse protocols and stimulus trains were used to assess synaptic vesicle release probability (Pr). Extracellular stimulation triggered excitatory glutamate receptor-mediated inputs onto recorded RGCs, as indicated by a reversal potential and pharmacology. Reducing excracellular [Ca^{2+}] reduced excitatory post-synaptic current (EPSC) amplitude and fits of the data showed that EPSC amplitude depended on extracellular [Ca^{2+}] with a Hill slope of ~5. The L-type Ca^{2+} channel blocker Nifedipine (1-30 μM) dose-dependently reduced type 6 CBC Ca^{2+} currents and RGC EPSCs. The relationship of EPSC amplitude and CBC Ca^{2+} currents was well fit with a Hill slope of ~1. In paired pulse experiments, inputs onto both On- and Off- RGCs were depressed with repeated stimulation, although On RGC inputs depressed more strongly. Train stimuli revealed that CBC inputs to On and Off RGCs have a Pr of ~0.9. The Ca^{2+}-dependence and nifedipine experiments suggest that CBC inputs onto alpha-RGCs operate with a conventional Ca^{2+} sensor with n = 5 and Ca^{2+} nanodomains, much like RBC inputs onto AII amacrine cells. Prominent short-term synaptic depression indicates that On and Off CBCs have a

high Pr. Differences between inputs to On and Off alpha-RGCs might have important implications for visual processing at CBC synapses.

Disclosures: M.J. Van Hook: None.

Poster

683. Retina: Photoreceptors and Outer Circuits

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VA grant 1 I01 BX002412

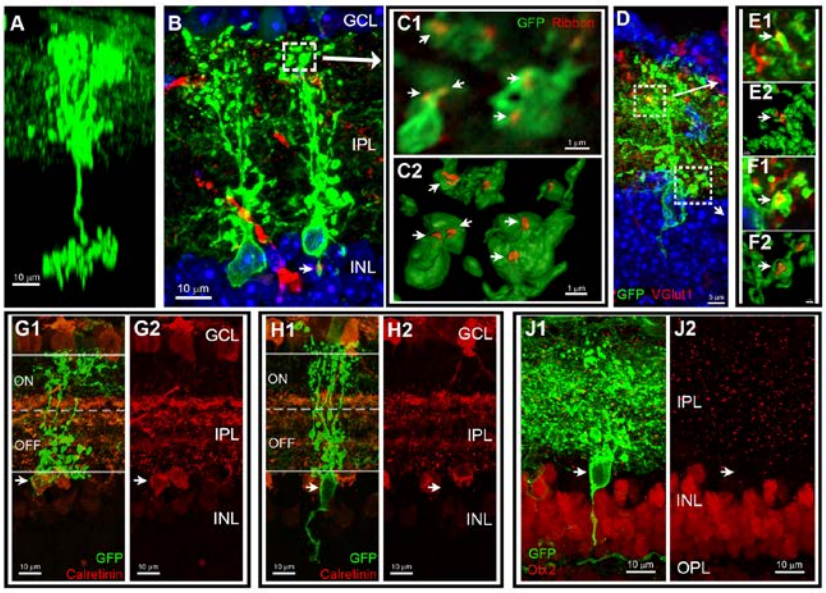
Research to Prevent Blindness (RPB)

Title: Crossing borders: A newly discovered, and unique subtype of bipolar cells provides excitatory input to both ON and OFF synaptic pathways in the retina

Authors: *B. K. YOUNG[1], C. RAMAKRISHNAN[3], P. WANG[2], K. DEISSEROTH[3], N. TIAN[2]
[1]Ophthalmology and Visual Sci., [2]Univ. of Utah, Salt Lake City, UT; [3]Bioengin & Psych, Stanford Univ. Dept. of Psychology, Stanford, CA

Abstract: In the retina, bipolar cells (BCs) process and transmit visual information from photoreceptors to retinal ganglion cells (RGCs) and amacrine cells (ACs). Traditionally, BCs have been divided into subtypes based on whether they receive their primary input from rod or cone photoreceptors, and where their primary synaptic output resides, either in the ON or OFF layer of the inner plexiform layer (IPL; Wassle et al., 2009). This classification produces 11 subtypes of cone BCs and 1 rod BC. Recently a new subtype of ON cone BCs has been discovered through the use of electron microscopy, implying the existence of more unidentified BCs (Helmstaedter et al., 2013). We utilize a novel transsynaptic technique with a Cre-dependent AAV2 WGA-Flpo:mCherry vector and a universal Flpo-dependent GFP transgenic mouse. Using this technique, we were able to identify a subtype of BC that has axonal terminals ramified in both the ON, and OFF layers of the IPL of the retina (see panels A and H1). We refer to this cell as an “Aii bipolar” cell (right cell in panel B) due to the similarity between the axonal processes of this cell to those of an Aii AC (left cell in panel B). However, immunohistochemistry analysis showed that Aii BCs contain ribbon synapses at their axonal terminal similar to other BCs, but unlike any AC (panel C). Ribbon synapses as well as vesicular glutamate transporter 1 (VGlut1) is expressed in the axonal terminals of the ON and OFF layer

ramifications (panels D-F). This indicates that they are excitatory neurons, unlike Aii ACs, and may release glutamate onto both ON and OFF RGCs, while all other cone bipolar cells synapse with RGCs either in the ON or OFF layer. Additionally, while Aii ACs express calretinin (panel G; Massey & Mills 1999), Aii BCs do not (panel H). The Orthodenticle Homeobox 2 gene (Otx2) has been used as a universal antibody marker for BCs (Park et al., 2017). However, Aii BCs do not express Otx2 (panel J). These results place Aii BCs in a singular position within the retina as the only subtype of BCs to have excitatory axonal projections that terminate in both the ON and OFF layers of the IPL.



Disclosures: **B.K. Young:** None. **C. Ramakrishnan:** None. **P. Wang:** None. **K. Deisseroth:** None. **N. Tian:** None.

Poster

683. Retina: Photoreceptors and Outer Circuits

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Topic: D.07. Vision

Support: DFG EXC 307

BMBF FKZ 01GQ1601

DFG BE 5601/1-1

DFG SCHU 2243/3-1

Title: Connectivity and computations of horizontal cells in the mouse retina

Authors: *C. BEHRENS[1,2,3,4], Y. ZHANG[4], T. EULER[1,2,3], P. BERENS[1,2,3], T. SCHUBERT[1,2]
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Abstract: In the mouse retina, short and medium wavelength-sensitive cone photoreceptors (cones) provide input to 13 types of cone bipolar cell (CBC). Additionally, one horizontal cell (HC) type provides feedback and feedforward input to cones and BCs, respectively. Although this general connectivity was described decades ago, a quantitative description of HC connectivity is lacking. Moreover, the computational role of HCs in the outer retina is still unclear: Recent studies suggest that - in addition to providing lateral, global feedback - HCs may also act on a local scale.
We approach these questions by exploiting recent high resolution imaging data: We reconstructed the dendritic trees of three HCs in a serial block-face electron microscopy (EM) volume (Helmstaedter et al., 2013). For this dataset, reconstructions of BCs and cone axon terminals are available from prior work (Helmstaedter et al. 2013; Behrens et al., 2016). Having reconstructed all cell types involved in the outer retinal circuitry, we went on studying the connectivity of HCs quantitatively.
Using an automatic classification procedure, we identified potential synaptic contacts at the cone pedicle base and manually analyzed contact points outside the cone pedicle. In addition to the well-known HC contacts in the cone axon terminal, we find a second site of potential synaptic contacts: Along all HC dendrites we observed “swellings” (bulbs), short segments of increased dendritic diameter. Each bulb featured one or two contacts to either bulbs of other HCs or to BC dendrites. We then built a biophysically realistic model of a HC dendritic branch. Incorporating detailed morphology and connectivity from EM data, the model allowed us to study the prerequisites for local processing in HC dendrites and the role of the bulbs in visual processing.
Our study adds quantitative data on HCs towards completing the outer retinal connectome. The anatomical observations hint at a complex functional role of HCs in the processing of cone signals. We may have identified a second synaptic layer in HCs and preliminary simulations suggest that the distinct morphological structure of HCs could easily support local processing.

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Poster

684. Retina: Inner Circuits and Ganglion Cells

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Plum Foundation

Title: GABA regulates presynaptic inhibition of mammalian cone photoreceptor Ca channels by modulating synaptic cleft pH

Authors: J. C. R. GROVE[1], A. A. HIRANO[1], N. C. BRECHA[1,2], *S. A. BARNES[3,1]
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Abstract: The goal of this study was determine how GABA contributes to the modulation of Ca channel currents in mammalian cone photoreceptors, to add to our understanding of how horizontal cells inhibit photoreceptors. This feedback signaling regulates the gain of the photoreceptor output synapse and contributes to the properties of the center-surround receptive field properties of downstream neurons in the retina and visual pathway. Numerous prior studies have made clear that the input to this pathway, e.g. horizontal cell membrane potential, drives actions that modulate the activity of presynaptic Ca channels in photoreceptors, the dynamic output of inhibitory feedback to cone photoreceptors. Here we identify the cellular mechanisms that come in between. One line of evidence suggests that GABA is responsible but that it acts not at cones but rather on horizontal cells, the same cells that release it, producing extracellular pH shifts that modulate photoreceptor Ca channel activation. Here we test key steps underlying this multistep feedback pathway by patch clamping horizontal cells and photoreceptors in mouse, rat and guinea pig retinal slices, first affirming electrophysiologically that block of GABARs produces pH-dependent disinhibition of cone Ca channels. We show that GABARs in horizontal cells mediate this disinhibitory action and that GABA depolarizes horizontal cells. The requirement of GABA release by horizontal cells in this action is confirmed by its absence using the Cx57-VGAT KO mouse. The effects are voltage dependent in two ways: 1) depolarization of horizontal cells increases GABA release and autoreception, and 2) depolarization decreases the driving force on HCO_3^- efflux, allowing basal acidifying processes to dominate cleft pH. Finally we reproduce the autaptic site-specific actions of GABA on cone Ca channels by targeted expression in horizontal cells of engineered anion channels (PSAM-GlyRs), which, activated by their orthogonal ligand, mimic the role of GABARs. Taken together, the present investigations validate our model in which 1) horizontal cells release GABA in a voltage-dependent manner, 2) autoreception via GABARs increases horizontal cell HCO_3^- conductance, 3) HCO_3^- efflux, driven by the horizontal cell membrane potential, buffers the pH of the synaptic cleft, and 4) cone Ca channels are modulated by pH-induced shifts of the voltage dependence of their activation.

Disclosures: J.C.R. Grove: None. **A.A. Hirano:** None. **N.C. Brecha:** None. **S.A. Barnes:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Topic: D.07. Vision

Support: NSF CRCNS Grant #DMS-1208027

UWIN postdoctoral fellowship

Title: Machine-learning-inspired approach to elucidate circuit dynamics and principles of parallel processing in the retina

Authors: *G. J. GUTIERREZ[1], F. M. RIEKE[2], E. T. SHEA-BROWN[2]
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Abstract: The retina is an adaptable neural circuit that processes an enormous range of inputs. Traditional models rely on static characterizations of retina circuit components, yet retinal ganglion cells are known to adapt not only their tuning but also the computations they perform [1-3]. Our goal is to understand how the retina optimally uses shared circuitry for different computations and to understand the circuit dynamics that underlie such changes in retinal processing. We've constructed a novel retina circuit model using an unconventional top-down approach that borrows from machine-learning [4]. A neural circuit is constructed from computational objectives rather than static circuit components to reveal the intrinsic neuron dynamics that generate flexible circuit computations. The model predicts functionally distinct currents that are needed to perform the simplest transformation of the circuit input. We then incorporate known biological features of the retina into the model, including a multi-dimensional structure that mirrors the parallel rod and cone pathways. Our ongoing work makes use of retina data to fit the model to conditions in which either rods or cones are activated alone. This will lead to more precise model predictions about the interaction between rod and cone pathways that produce retina-specific computations.

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Disclosures: G.J. Gutierrez: None. **F.M. Rieke:** None. **E.T. Shea-Brown:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Topic: D.07. Vision

Title: Epoxyeicosatrienoic acid (EET)-mediated retinal functional hyperemia enhanced by inactivation of TRPV4 channels

Authors: *D. Y. TS'O[1], M. BEGUM[1], T. T. T. PHUONG[2], D. KRIZAJ[2]
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Abstract: Intrinsic signal optical imaging (ISOI) has considerable potential to non-invasively monitor retinal function in health and disease. The imaged response observed with ISOI has been shown to reflect the change in local blood flow due to light stimulation of rod photoreceptors, but the precise mechanisms underlying this chain of events remains unclear. Arachidonic acid (AA) metabolites including the EETs, 20HETE and prostaglandin having been shown as key mediators of neurovascular coupling but their contribution to light-evoked retinal hemodynamics *in vivo* is largely unexplored. Using ISOI in cat retina, we investigated the contributions of these AA metabolites on light-induced retinal hemodynamics via intravitreal injections of agents that specifically target these signaling pathways. We found that the inhibition of EET production via the agent PPOH (20uM) eliminated the stimulus-driven imaged response, indicating that EET is a critical intermediary in regulating light-activated retinal blood flow. One possible pathway of EET signaling is via its binding site on TRPV4, a shear flow-activated cationic channel. Immunocytochemistry showed TRPV4 expressed in human retinal microvascular endothelial cells and glial endfeet. The channel was activated by AA (10uM), 5'6-EET and 11'12-EET, and inhibited by antagonists of phospholipase A2. Intravitreal injection in cat of a selective TRPV4 agonist GSK1016790A (10nM) induced a marked vasodilation, (~25% reduction in retinal reflectance). In contrast, an injection of the antagonist HC067047 yielded a vasoconstriction (~10% increase in retinal reflectance). GSK1016790A also abolished the light-stimulated imaging signal, while HC067047 increased this signal. The action of GSK1016790A on the imaged signal is similar to other vasodilators (e.g. nifedipine) that reduce or abolish these signals by saturating the vasodilatory range of the vasculature. These results demonstrate the TRPV4 plays significant role in the control of retinal vascular tone. However, since TRPV4 inhibition increased the stimulus-driven retinal imaging signals, its role in the light-evoked signal is likely to be secondary. These studies help elucidate the underlying mechanisms of the ISOI technique in the retina and of retinal functional hyperemia.

Disclosures: **D.Y. Ts'o:** None. **M. Begum:** None. **T.T.T. Phuong:** None. **D. Krizaj:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Topic: D.07. Vision

Support: BPI project : Sight Again

Title: Long term visual restoration using optogenetic engineering of retinal ganglion cells with AAV2.7m8-ChrimsonR-td-Tomato

Authors: *G. GAUVAIN[1], H. AKOLKAR[1], A. CHAFFIOL[1], R. CAPLETTE[1], C. JAILLARD[2], E. BRAZHNIKOVA[2], M. DESROSIERS[2], D. PRUNEAU[3], J. DUEBEL[1], R. BENOSMAN[1], D. DALKARA[2], J. SAHEL[2], S. PICAUD[1]
[1]Dept. of Information Processing, [2]Fondation Voir & Entendre - Inst. De La Vision, Paris, France; [3]Gensight Biologics, Paris, France

Abstract: Retinitis Pigmentosa (RP) is a collection of inherited dystrophies with similar clinical features resulting in the progressive loss of photoreceptors leading to blindness. Although gene therapy is currently in clinical trial for hereditary dystrophies, the considerable genetic heterogeneity in RP preclude the rapid development of treatments for patients. In this pre-clinical study we are considering an alternative to classic gene therapy and propose to use viral vector to deliver a microbial opsin, ChrimsonR, to optically control surviving retinal ganglion cells. We previously selected AAV2.7m8-ChrimsonR-tdTomato as the most potent of our viral constructs. We investigated here in nonhuman primates the treatment efficacy after long term (6 month) expression of our transgene, for three viral doses. None of the injected primates developed significant immune response or sign of morphological alteration based on the fundus images. We performed ex-vivo retinal ganglion cells (RGCs) recordings on 256 electrode multielectrode arrays (MEA). We isolated the response of RGCs expressing our construct from natural light response using pharmacological blockers (L-AP4, CNQX, CPP). We stimulated retinas using a digital micro mirror device (DMD) with a light source centered at 600nm (+/-20nm) allowing for: 1) full field stimuli of various durations, and 2) patterned stimulation (small spots, moving bar and objects). We also used a variable wavelength source in order to determine spectral sensitivity. Our result indicates the highest viral does as optimal for best efficacy in term of transduction efficiency (evaluated through overall induced activity on the MEA, and post-fixation cell counting on confocal images) . We also demonstrate excellent spatio-temporal sensitivity of the reactivated retina (responses for spot as small as 50µm) as well as extremely short delay of responsiveness (~10msec for first evoked action potential). In combination of MEA recordings we did 2-photon guided single cell patch clamp experiments (whole cell and cell attached) to directly measure photocurrent induced by our opsin. These different

experiments demonstrate stable expression of ChrimonR-td-Tomato in non- human primates on a 6 month period post-infection, they also provide evidence for functional efficacy at doses, which could represent the therapeutic dose range for the future clinical trial.

Disclosures: **G. Gauvain:** None. **H. Akolkar:** None. **A. Chaffiol:** None. **R. Caplette:** None. **C. Jaillard:** None. **E. Brazhnikova:** None. **M. Desrosiers:** None. **D. Pruneau:** A. Employment/Salary (full or part-time):; GenSight Biologics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GenSight Biologics. **J. Duebel:** None. **R. Benosman:** None. **D. Dalkara:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GenSight Biologics. F. Consulting Fees (e.g., advisory boards); GenSight Biologics. **J. Sahel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GenSight Biologics. F. Consulting Fees (e.g., advisory boards); GenSight Biologics. **S. Picaud:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GenSight Biologics. F. Consulting Fees (e.g., advisory boards); GenSight Biologics.

Poster

684. Retina: Inner Circuits and Ganglion Cells

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 684.05/FF8

Topic: D.07. Vision

Title: A high threshold, NMDA-dependent input drives retinal dopamine release in response to light

Authors: *J. W. MORLEY, V. PEREZ-FERNANDEZ, M. A. CAMERON
Med., Western Sydney Univ., Sydney, Australia

Abstract: Adaptation of the retina to the presenting light conditions relies considerably on modulation of retinal pathways by dopamine (DA). DA is released by a unique set of neurons known as dopaminergic amacrine cells (DACs). Cones, rods and intrinsically photoresponsive retinal ganglion cells (ipRGCs) have been shown to input DACs. However, measurement of dopamine release in the retina in response to light does not align with electrophysiological and/or immunohistochemical reports. The purpose of this study was to describe the photoreceptive origin of light-induced dopamine release using pharmacology and transgenic/mutant mouse models. We used UHPLC-MS/MS analysis to quantify DA released from the mouse retina in an *ex vivo* preparation in response to 4 light intensities (max 1.6 log W/m^2; ~10,000 lux). Wild-type, $Gnat2^{A517G}$ (cone-functionless), and *rd/rd* (lacking rods and cones) animals were light pulsed and pharmacological blockers applied. We found that light caused a significant increase in dopamine

release in the retinae of both wild-type and *Gnat2*^{A517G} mice but only at very bright light intensities (> 0.65 log W/m^2; ~1000 lux). In agreement with previous studies, no significant increase was obtained in response to light in *rd/rd* mice at any light intensity. The gap junction blocker MFA (1mM) caused a significant reduction in light induced DA release in both wild-type and *Gnat2*^{A517G} animals, but did not completely abolish the light-induced increase in comparison to dark conditions. While the glycine receptor blocker strychnine (10μM) did not affect dopamine release in either light or dark, the $GABA_{A/C}$ receptor blocker picrotoxin (100μM) caused a significant DA increase in both light and dark in wild-type mice. Surprisingly, the NMDA channel blocker AP5 (50μM) completely abolished light induced DA release in the wild-type mouse, suggesting a pivotal role for NMDA receptors in this response. While all our data thus far support the theory that rods are driving the light-induced release of DA, the threshold for this response is far (6 log units) above the rod threshold. We hypothesize that the NMDA input originates from ipRGC photoreceptors that are only effective when paired with inputs from the outer retina, allowing this input to be "gated" at such a high intensity. Thus both outer retinal (predominately rods) AND ipRGCs are required for light induced DA release.

Disclosures: J.W. Morley: None. **V. Perez-Fernandez:** None. **M.A. Cameron:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Topic: D.07. Vision

Support: FET Grant 600847 : RENVISION

Title: High spatial resolution recordings reveal the contribution of long-range horizontal inhibition in modulating light-evoked responses of ON and OFF retinal ganglion cells

Authors: *F. BOI[1], D. LONARDONI[2], S. DI MARCO[4], A. MACCIONE[3], L. BERDONDINI[5]
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Abstract: The retina encodes visual sensory inputs into spike trains by processing information through five main layers where reside more than 60 different cell types. This processing is performed by parallel vertical circuits (from photoreceptors down to ganglion cells) that are modulated by horizontal inhibitory connections. However, the contribution of such long-range horizontal inputs remains not completely understood. High-resolution CMOS multielectrode arrays (4096 electrodes arranged in a 64x64 array, 42 μm electrode pitch) permit simultaneous spiking activity recording of more than 3'000 single retinal ganglion cells (RGCs) all over the

entire retina. By providing fine spatial and temporal sampling capabilities, these devices offer novel opportunities to investigate the effects of horizontal long-range network interactions (such as provided by wide-field amacrine cells) in modulating the spiking activity of RGCs during visual stimulation. Here, by combining these recording capabilities with a visual stimulator that enables micrometric and sub-millisecond spatiotemporal precision, we present results obtained by studying the effects induced by the spatial confinement of visual stimuli. The stimuli consisted in white/black flashes and moving bars of different spatial gratings (range of 0.026-0.75 cycle/deg), both presented at 1Hz stimulation frequency. We compared ON and OFF RGCs population responses of different retinas (n=4), both under full-field (FF, visual stimulus projected on the entire retina) and spatially confined "masked" stimuli (M, i.e. the same visual stimulus projected on an area of the retina). We found that flashes projected under the M condition gave rise to delayed ON and OFF RGCs responses (~30 ms) with respect to the FF stimulation condition. We further observed that OFF responses delay was strongly dependent to the stimulus contrast while the ON RGCs responses were always delayed regardless of the contrast. A similar trend was also observed by analyzing the spiking activity in response to moving bars presented under both M and FF conditions. Our results reveal that variations of the RGCs spiking activity dynamic in response to confined stimuli are most likely not only the result of vertical and local processing circuitries, but are also modulated by horizontal processing circuits carrying information from far regions of the retina. This observation was further confirmed by experiments showing that these differences in ON and OFF responses to visual stimuli under M and FF conditions disappeared under bicuculline, thus suggesting a potential role of wide-field amacrine cells in mediating the RGCs response delay.

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Poster

684. Retina: Inner Circuits and Ganglion Cells

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Gruber Science Fellowship

Title: Optogenetic stimulation reveals type- and target-specific computations at genetically-identified amacrine cell synapses

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Abstract: Recent work in the vertebrate retina has begun to provide insight into the receptive field properties, anatomical organization, and functional roles of the ~40 types of amacrine cells (ACs). However, while several AC types have been identified as critical sources of synaptic inhibition in specific retinal circuits, the precise computational and functional properties of AC synapses, and the extent to which these properties differ between AC types, remain largely unknown. Here, we develop an optogenetic approach to probe the synaptic properties of genetically-identified ACs in the wholemount mouse retina. To control presynaptic membrane potential (V_{pre}) of specific AC types, we conditionally expressed channelrhodopsin-2 (ChR2) using the Cre-Lox system. Current clamp recordings from ChR2-expressing CRH-1 ACs and starburst ACs (SACs) during optogenetic stimulation revealed fast, linear modulation of V_{pre}. Subsequent voltage clamp recordings from ON α ganglion cells (GCs) clamped at 0 mV during CRH-1 AC stimulation exhibited similarly linear inhibitory postsynaptic currents (IPSCs). By contrast, voltage clamp recordings from ON-OFF direction-selective GCs (ooDSGCs) clamped at 0 and -70 mV during SAC stimulation revealed strong rectification of both GABAergic IPSCs and cholinergic excitatory PSCs, respectively. To quantify differences in rectification and temporal filtering, we constructed linear-nonlinear (LN) models of PSCs recorded from GCs during optogenetic white-noise stimulation of presynaptic ACs. In addition to type-specific differences in PSC rectification, LN analysis also revealed distinct temporal filtering properties at each AC synapse: compared to SAC—ooDSGC synaptic filters, CRH-1 AC—ON α GC filters peak earlier and initially decay more rapidly. Surprisingly, we found that SAC—ooDSGC IPSCs exhibit stronger rectification and slower temporal filtering than SAC—SAC IPSCs, demonstrating that a single AC type can perform parallel synaptic computations in a target-specific manner. Finally, application of isradipine, a selective L-type voltage-gated calcium channel (VGCC) blocker, abolished ChR2-mediated IPSCs at CRH-1 AC—ON α GC synapses but not SAC—ooDSGC synapses, suggesting that distinct VGCC types mediate GABA release at these synapses. Taken together, these results show that AC synapses possess diverse computational properties that may be critical for shaping visual processing in retinal circuits.

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Poster

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Title: Satb1 regulates Contactin5 to construct a bistratified dendritic arbor in retina

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Abstract: The size and shape of dendritic arbors are prime determinants of neuronal connectivity and function in the central nervous system. In the retina, for example, dendrites of different types of retinal ganglion cell (RGC) are confined to one or a few of ~10 strata within the inner plexiform layer, restricting the interneurons from which they receive inputs, and thus the visual features to which they respond. ON-OFF direction-selective RGCs (ooDSGCs) have bistratified dendrites, in which ON inputs that trigger responses to light-onset and OFF inputs that trigger responses to light-offset are segregated to inner and outer strata, respectively. Here, we describe a transcriptional program that controls assembly of the ON arbor. We found that the transcriptional regulator Satb1 is expressed by ooDSGCs but few other RGCs. In *Satb1* mutant mice, ooDSGCs become monostratified, lacking ON arbors but retaining OFF arbors. As a consequence, they lack ON responses, but there is no detectable effect on OFF visual responsiveness or direction selectivity, indicating that Satb1 specifies a discrete visual feature. To seek mediators of this effect, we compared transcriptomes of control and Satb1-deficient ooDSGCs. We found that Satb1 regulates expression of a homophilic adhesion molecule, Contactin 5 (*Cntn5*), and that *Cntn5* mutants partially phenocopy *Satb1* mutants. We then found that both Cntn5 and its co-receptor Caspr4 are expressed not only by ooDSGCs but also by ON starburst amacrine cells, an interneuronal type that form a scaffold on which ooDSGC ON dendrites fasciculate. Conditional knockdown of Cntn5 in either presynaptic interneurons or postsynaptic ooDSGCs leads to the same defect as constitutive Cntn5 loss, supporting the idea that Cntn5-mediated homophilic interactions of ooDSGCs with ON starburst amacrines are required for maturation or maintenance of ooDSGC ON dendrites. Thus, Satb1 acts in part through Cntn5 to direct formation of a specific portion of the ooDSGC dendritic arbor that enables these RGCs to respond to ON stimuli.

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Poster

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University of Innsbruck, Center of Molecular Biosciences (CMBI)

Title: Retinal electrophysiology in a mouse model of multiple system atrophy

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Abstract: Multiple System Atrophy (MSA) is a neurodegenerative disease with proposed causal involvement of α-Synuclein (α-SYN) aggregate formation. In Parkinson's disease (PD), another α-Synucleinopathy, visual symptoms such as diminished contrast sensitivity are well described while for MSA visual manifestations have thus far not been prominent. In the clinical examination of patients, visual tests are an important tool to distinguish PD and MSA. Our experiments are aiming to determine the visual function of a MSA mouse model. In this mouse model of human α-SYN overexpression we detected strong aggregation of α-SYN in the retina. Therefore we set out to determine the effect of the α-SYN aggregation on retinal physiology and function.
We used transgenic mice, expressing human α-SYN under the proteolipid protein promotor (PLP-α-SYN) and corresponding wild type (WT) controls of two months of age. Mice were dark adapted and retinas were extracted under dim red light. Retinal ganglion cell spiking responses and retinal local field potentials ("in vitro ERG") were recorded using micro-electrode arrays (MultiChannel Systems MEA2100), while the retina was stimulated with a variety of visual stimuli designed to test contrast sensitivity. The stimuli included flashes, sinusoidal full field stimuli and drifting gratings, with different contrasts each. Visual stimulation was done at two distinct light levels achieved through the insertion of neutral density filters. The light levels corresponded to scotopic and photopic luminance ranges.
In vitro ERG responses to full field flashes of different contrasts showed no difference between WT and PLP-α-SYN retinas. However, we found significant changes in a frequency modulated sinusoidal stimulus which were light level-dependent. While the scotopic responses were comparable, the photopic responses of PLP-α-SYN retinas were significantly more delayed ($0.023 < p < 0.048$, Wilcoxon ranksum test; WT 81.5 ± 7.8 ms, PLP-α-SYN 114.1 ± 7.9 ms; means of 29 peaks ± std). Retinal ganglion cell responses in PLP-α-SYN mice on the other hand were comparable to WT both in frequency domain modulation as well as in ganglion cell contrast sensitivities.
The unchanged flash in vitro ERG highlights that outer retinal function of PLP-α-SYN animals is not severely impaired. The lack of a strong impact on ganglion cell responses conforms to the normal visual function in MSA patients. The changes in the in vitro ERG to frequency

modulation however revealed a so far unknown functional change that could be a potential diagnostic marker that might also be tested in human patients.

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Poster

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Title: Quantifying protein synthesis and axonal transport in the visual system and its response after optic nerve injury

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Abstract: How do protein synthesis and axon transport contribute to neuronal circuit development or to response to injury? To study this question in specific visual circuits and in response to pathological processes, we have developed new strategies for analyzing proteome translation in the retina and its axonal transport in the optic nerve (ON) to the lateral geniculate nucleus (LGN) or the superior colliculus (SC) (Schiapparelli et al 2014). We are using these methodologies to address two main questions: (a) as LGN and SC projections are involved in distinct visual functions, is the protein “transportome” to the LGN different from that to SC? And (b) how are protein synthesis and axonal transport affected in response to optic nerve injury? To address the developmental transportome, we labeled the retina in vivo with NHS-biotin, which tags pre-existing proteins. We found that the population of proteins transported to LGN or SC are highly overlapping, but some of these molecules are selectively sent to a specific target. Future experiments will uncover how differential targeting leads to differential downstream signaling in different neuronal circuits, determining specific function. To examine response to injury, we labeled newly synthetized proteins the retina with azidohomoalanine (AHA) following optic nerve crush (ONC) in adult rats, and identified ~30 proteins whose synthesis and subsequent transport to ON significantly changes 27 hours after ONC. To examine the transportome after injury, after NHS-biotin retinal labeling we identified ~300 proteins whose transport down the optic nerve decreased after ONC, and ~30 whose transport increased

after the 12 hours of ONC. Extending this methodology to glaucomatous injury will allow us to identify and quantify differentially translated and transported proteins in RGCs in the context of disease. We hypothesize that understanding whether specific proteins are synthetized and transported to an injury site will lead to new understanding of pathophysiology of injury and new approaches to promoting regeneration.

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Poster

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Title: Extracellular pH changes mediated by retinal Muller glia are shaped by two distinct molecular pathways

Authors: *M. A. KREITZER[1], B. K. TCHERNOOKOVA[2], D. SWYGART[1], C. HEER[1], M. GONGWER[1], L. SHEPHERD[1], H. CARINGAL[1], R. P. MALCHOW[2]
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Abstract: Alterations in extracellular H+ are correlated with significant changes in the release of neurotransmitter in the retina. This has led to a number of recent studies examining the role extracellular H+ dynamics play in shaping visual signals. However, few studies have directly measured H+ fluxes from individual identified cells. Self-referencing H+ selective microelectrodes have proven to be ideally suited for sensing extracellular pH changes from isolated cells. Two recent studies utilized self-referencing to measure H+ fluxes from retinal Müller glia, isolated from tiger salamander retina. These studies characterized two pathways by which Müller cells regulate extracellular pH. In the first pathway high KCl applied to Müller cells produces a large HCO_3^- dependent extracellular acidification at the endfoot. In the second

pathway application of extracellular ATP also induces a large HCO_3^- independent extracellular acidification. These studies, when coupled to a growing interest regarding the roles glial cells play in shaping synaptic transmission, bring an important focus on elucidating roles retinal glia play in shaping the pH of the extracellular environment. The present study directly examines overlap of the two previously reported regulatory pathways by measuring extracellular H+ fluxes using self-referencing H+ selective microelectrodes positioned adjacent to the endfoot of isolated Müller cells, while in a HCO_3^- buffered Ringer's solution. Externally applied 50 mM KCl induced an increase in H+ flux. 100 µM ATP led to a large additional H+ flux while the cell was bathed in high KCl. The H+ flux could be stepped back to control levels by first removing ATP followed by wash-off of the high KCl. The independence of these two pathways inducing acidification outside of the endfoot were further supported by Ca^{2+} imaging studies using the intracellular Ca^{2+} indicator Oregon Green BAPTA 1-AM. These trials demonstrated that high KCl induced an intracellular calcium rise that was dependent on extracellular calcium and not intracellular stores. ATP also induced an intracellular calcium rise but the rise occurred independent of the presence of extracellular Ca^{2+} and could be abolished when intracellular stores were emptied. Additionally, the increase in extracellular H+ mediated by ATP was calcium-dependent but the KCl-induced acidification was not. Collectively, these findings demonstrate that retinal Müller cells have two distinct pathways through which they regulate extracellular pH around the cell, and these findings also point toward a multifaceted ability of Müller cells to regulate pH and by extension shape synaptic transmission in the retina.

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Poster

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Title: Determining the role of pre-synaptic NMDA Receptors in retinofugal topographic map formation

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Abstract: Efficient processing of sensory information is a critical function of the nervous system. Deficits in sensory processing and integration are commonly seen in

neurodevelopmental disorders such as autism and fragile X syndrome. In the visual system, neurons are organized topographically, such that neighboring neurons monitor adjacent regions of space. Retinal ganglion cells (RGCs) project topographically to the superior colliculus (SC) and dorsal lateral geniculate nucleus (dLGN). The establishment of topography in both the SC and the dLGN is dependent on spontaneous correlated activity. However, the mechanisms by which activity mediates topographic map formation remain unclear. Previous studies suggest that N-methyl-D-aspartate receptors (NMDARs) play a critical role in the establishment of topography by RGCs; however, it is unclear if they are required pre- or post-synaptically. To determine the role of pre-synaptic NMDARs in retinofugal topographic map formation, we used a conditional genetic strategy to specifically ablate NMDAR function in RGCs. We focally labeled RGCs and visualized the termination zone (TZ) of their projections in the SC and dLGN. Our preliminary data suggests that there was no change in TZ size in the SC, but TZs appeared to be larger in the dLGN. Bulk labeling of all RGCs in both eyes of these mice showed that eye-specific lamination was similar to controls, suggesting this activity-dependent process is unaffected in the absence of pre-synaptic NMDARs. Together, these data suggest that retinogeniculate topographic map formation may require pre-synaptic NMDAR activity, whereas retinocollicular map development may not. While our data do not suggest a role for pre-synaptic NMDARs in retinocollicular topography, we cannot rule out a role in the development of proper visual receptive fields. Thus, our future studies will explore visual function in the SC and dLGN to determine the role of pre-synaptic NMDARs visual circuit formation.

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Poster

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Title: Focal electroretinogram and visual evoked potential in rats

Authors: *A. GROSS, N. FARAH, Y. MANDEL
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Abstract: Purpose: Measurements of focal retinal function is helpful in evaluation localized retinal malfunction and in assessing intervention efficiency in treatment modalities such as retinal prostheses, genetic therapy or stem cell transplantation. In this work we characterized the focal Electroretinogram (fERG) and Visual Evoked Potential (fVEP) in response to a photopic localized visual stimulus projected on pigmented rat retina.
Methods: fERGs and fVEPs signals were recorded in Long-Evans anesthetized rats in response to visual stimulus consisted of LED flashes relayed through circular apertures which are

incorporated into a fundus camera (Micron IV, Phoenix Research Lab) optical path. Stimuli with varying irradiances, repetition rates, and spot diameters ranging from 0.5 to 3.0 mm were investigated at various background illumination. VEP signals were recorded using screws electrodes implanted over the primary visual cortex and ERG signals were recorded using a corneal contact electrode.
Results: The fERG b-wave amplitude increased with light intensity reaching a plateau at $4*10^3 cds/m^2$, and decreased with increasing stimuli repetition rate and increasing background illumination. The fVEP amplitude (N1P2) demonstrated a similar trend, however, a plateau was observed at a lower stimuli luminance ($1*10^3 cds/m^2$) suggesting a smaller cortical dynamic range as compared to the retina. fERG and fVEP b-wave amplitude increased with stimuli spot size reaching a plateau at smaller spot size for high intensity illumination levels, suggesting a contribution of the scatter effect. The b-wave latency decreased with increasing stimuli luminance, reaching a minimum at luminance levels above $10cds/m^2$. The photopic stimuli elicited a robust photopic negative response (PhNR) with increasing amplitude and latency for increasing stimuli irradiance and spot size.
Conclusions: The effect of various retinal focal stimuli parameters on fERG and fVEP signals in normal pigmented rats show characteristic responses. A robust PhNR component was found and characterized. Evidences for a scatter effect were found at high irradiance stimuli, which could be reduced by addition of background illumination. In addition, our results demonstrate the larger retinal dynamic range as compared to the cortical dynamic range under photopic conditions. This study can serve as a basis for evaluating localized retinal function as an important research tool for investigating retinal diseases in rodents.

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Poster

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Title: Exploring synaptic and computational properties of starburst cells through altered neuronal morphology

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Abstract: Direction selective ganglion cells in the mammalian retina fire action potentials maximally to objects moving in a preferred direction, but minimally to objects moving in the opposite, or null, direction. These directional responses are produced by an asymmetry in overall inhibitory conductance, such that object motion in the null direction elicits a greater amount of GABAergic inhibition onto direction selective cells. How does this asymmetry emerge? Starburst amacrine cells are axonless interneurons in the retina that are required for direction selectivity and are characterized by their radially symmetric dendritic arbors. The ends of these dendrites form GABAergic synapses onto direction selective cells, providing asymmetric GABAergic inhibition via two components: 1) directionally selective responses in starburst cell dendrites themselves, in which motion away from the starburst cell soma elicits a larger depolarization at GABA release sites than motion toward the starburst cell soma and 2) a selective wiring process between starburst cells and direction selective cells.
To determine how the “starburst” morphology of these cells enables and contributes to the mechanisms responsible for these directional responses, we utilized mice lacking the Sema6A signaling molecule, whose starburst cells no longer display radial symmetry (Sun et al., 2013), and whose ganglion cells have reduced direction selectivity. Using paired recordings and both subcellular and population level 2-photon Ca^{2+} imaging, I will present results describing how the morphological defects in these starburst cells impact the computation of direction selectivity at multiple levels within the retinal direction selective circuit.

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Poster

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ARCS Foundation, Seattle Chapter

Title: Disentangling multiple sources of variability in the responses of retinal ganglion cells

Authors: *A. I. WEBER[1], E. SHEA-BROWN[2,3,4], F. RIEKE[3]
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Abstract: As our sensory systems encode information about the world around us, the relevant signals are corrupted by noise at several different stages.[1] Noise present in the stimulus itself, such as in stochastic photon arrival at the retina, corrupts the signal before it is encoded. Additional noise is added by a variety of biological processes, such as ion channel opening, vesicle release, and neurotransmitter diffusion. This noise not only places fundamental limits on the accuracy with which information can be encoded, but additionally dictates which processing strategies will be most effective in transmitting signal relative to noise.[2,3] Understanding the nature of noise in a neural circuit is therefore critical to interpreting its function.
Despite the many sources of noise present in biological circuits and the importance of understanding this noise, current models of neural responses typically assume a single source of variability, such as Poisson spike generation. Here, we present a framework to disentangle the contributions of multiple sources of variability in the responses of retinal ganglion cells. We record the spiking responses of ON alpha ganglion cells in the mouse retina to a flickering light stimulus under several different levels of ambient illumination. Then, using a flexible statistical model that incorporates multiple biologically feasible sources of noise, we determine the relative contributions of these noise sources using maximum likelihood estimation. Importantly, this work provides an approach to extend classical models, such as linear-nonlinear and generalized linear models, to include more biologically accurate sources of variability.
Using this new framework, we find that the relative contributions of different noise sources change with light level, suggesting that retinal ganglion cells ought to flexibly adapt their processing strategies in order to efficiently encode information under these different conditions.

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Poster

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Title: Dynamic modeling and functional analysis of *Drosophila* chromatic circuit

Authors: *T. BISWAS[1], C.-H. LEE[2], Y. LI[2]
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Abstract: In Drosophila, UV (ultraviolet light) detection is mediated by UV-sensing R7 photoreceptors and their downstream amacrine neuron Dm8. Inactivation of R7s or Dm8 neurons abolished animals' innate preference to UV light over green light. Using calcium imaging to monitor neuronal activity, we found that UV illumination excited R7 photoreceptors but inhibited Dm8 neurons, consistent with our previous findings that Dm8 receives inhibitory histaminergic inputs from R7s. However, Dm8's responses exhibited additional properties: This includes OFF-excitation where after the UV stimulus is removed, the Dm8's do not directly relax to their normal state but rather become excited, and only slowly relax to their natural state thereafter. Also Dm8's exhibit center-surround antagonism, *i.e.* the Dm8's, that are "adjacent" to the Dm8 receiving inhibitory inputs from stimulated R7's, become excited. These features cannot be readily explained by known circuits. To gain more insight we take a "dynamical systems" approach involving first order differential rate equations to model the first few stages of the visual circuit. Based on our simulations and genetic manipulations, we suggest that Dm8's responses may be significantly shaped by a feedback inhibitory circuit.

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Poster

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Title: Microstructural white matter abnormalities and the correlations with RNFL thickness in different severity of normal tension glaucoma: An atlas-based diffusion tensor analysis study

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Abstract: Purpose**:** To detect white matter (WM) damage and investigate the correlations between DTI parameters and retinal nerve fiber layer (RNFL) thickness in normal tension glaucoma (NTG) patients using diffusion tensor imaging (DTI).
Materials and Methods: 47 patients with NTG and 15 normal control (NC) subjects underwent DTI scanning and ophthalmological examination. Based on mean deviation scores (MDS) on visual field testing, the NTG patients were divided into three subgroups for comparison with the NC group: mild (mi-NTG, n = 18), moderate (mo-NTG, n = 14), and severe (se- NTG, n = 15) NTG. Atlas-based analysis (ABA) was performed on each subject to measure fractional anisotropy (FA) and mean diffusivity (MD). Association between DTI metrics and the severity of the disease (RNFL thickness) was studied using linear mixed regression analyses.
Results: Compared with NC subjects, significantly decreased FA and increased MD were observed in left anterior corona radiate (L.ACR), bilateral posterior thalamic radiation (B.PTR), bilateral sagittal stratum (B.SS), bilateral fornix/stria terminalis (B.FX/ST), bilateral tapetum (B.TAP), body of corpus callosum (BCC) and genu of corpus callosum (GCC) (all $p<0.05$). Further subgroup analyses revealed that the mi-NTG subgroup had significantly decreased FA and increased MD only in the B.PTR ($p<0.05$), the mo-NTG subgroup showed declined FA and increased MD in the B.PTR, BCC, GCC (all $p<0.05$); the se-AD subgroup exhibited lower FA and higher MD values in all these WM regions (all $p<0.05$). Furthermore, FA and MD values in these WM regions displayed good correlations with RNFL thickness ($p<0.05$), especially for the FA values in the B.PTR ($r=0.608$, $p<0.01$).
Conclusions: There are microstructural differences between different severity of NTG patients and normal controls in visual related WM regions, which could be used for the early diagnosis of NTG and monitoring disease progression.

Disclosures: Z. Tang: None. **X. Sun:** None. **R. Wang:** None. **Z. Xiao:** None. **L. Wu:** None. **Y. Zhong:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 684.18/FF21

Topic: D.07. Vision

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Leverhulme Trust RPG-2016-315

Newcastle University Faculty of Medical Sciences

Title: Functional characterisation of parvalbumin-expressing cells in the mouse retina

Authors: *E. SERNAGOR, G. HILGEN
Newcastle Univ., Newcastle Upon Tyne, United Kingdom

Abstract: It is well established that the Ca^{2+} binding protein parvalbumin (PV) is expressed in many retinal ganglion cells (RGCs) and amacrine cells (ACs). However, virtually nothing is known about their functional correlates. We have investigated the functional properties of PV-expressing cells in the mouse retina using pharmacogenetics, based on silencing (hyperpolarizing) PV neurons with Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in the presence of the DREADD agonist clozapine N-oxide (CNO). A high-density large-scale MEA (Biocam, 3Brain) featuring 4096 electrodes covering most of the mouse retina was used to study light-evoked responses from 100s-1,000s RGCs simultaneously. Various stimuli were used to characterize RGC receptive field organization and direction/orientation selectivity (DS, OS) in control conditions and in the presence of CNO (2μM). RGCs with >50% decrease in activity in CNO were classified as PV-RGCs and were compared to all other RGCs (non-PV RGCs). The role of PV-expressing ACs was established by comparing how non-PV RGCs respond to light without and with CNO. Overall, we found a high incidence of OFF transient cells (17.5%) amongst PV RGCs, whereas non-PV RGCs tend to have a higher incidence of ON transient responses (19.8%). We used the bias index (BI) to classify RGCs into ON (0.33<BI<1), OFF (-1<BI<-0.33) and ON-OFF cells (-0.33<BI<0.33). The BI for PV RGCs is close to 0 (-0.039) whereas in non-PV RGCs it is significantly skewed towards ON values (0.37). The duration of ON and OFF responses are both over 30% longer in PV RGCs. There was a massive increase in baseline activity in all non-PV RGCs in the presence of CNO. Their average BI increased to 0.67; ON and OFF responses became respectively 9.2 and 20.7% longer and the difference in duration between transient and sustained responses became less distinct. Both DS and OS (quantified by the DS and OS index) decreased by ~50% and the total number of spikes elicited by moving stimuli increased by ~50% in DS/OS cells. Interestingly, there was no change in motion elicited spike numbers in non-DS/OS RGCs. Finally, we found that oscillations induced in RGCs during specific visual tasks became much stronger in the presence of CNO. Our observations suggest that PV-RGCs tend to respond more to stimulus offset and their responses are relatively long. PV-expressing ACs mediate OFF responses and they gate both ON and OFF responses. They are strongly involved in establishing DS/OS, presumably by providing a robust direct or indirect asymmetric inhibitory input specifically onto DS/OS cells. Finally, they appear to control oscillatory activity between RGCs during specific visual tasks.

Disclosures: **E. Sernagor:** None. **G. Hilgen:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Support: 1DP2EY022584

Klingenstein-Simons Fellowship in the Neurosciences

Karl Kirchgessner Foundation Vision Research Grant

Northwestern University

Title: Melanopsin sets the contrast detection threshold for M4 ipRGCs

Authors: *T. M. SCHMIDT, T. SONODA, S. LEE
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Abstract: Melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs) have traditionally been associated with subconscious visual behaviors such as circadian photoentrainment and the pupillary light reflex. However, mounting evidence from *in vivo* electrophysiological recordings and behavioral experiments suggests that melanopsin phototransduction in ipRGCs also plays an important role in pattern vision. The cellular mechanisms underlying this influence have not been examined. Because melanopsin has been shown to be necessary for normal behavioral contrast sensitivity, even in the presence of fully functional rod and cone photoreceptors, we examined how melanopsin phototransduction influences the signaling properties of M4 ipRGCs. M4 ipRGCs are more commonly known as ON alpha RGCs, which are highly sensitive to contrast and project to image forming targets, making these cells good candidates for influencing behavioral contrast sensitivity. Consistent with a role for melanopsin in behavioral contrast sensitivity, when we directly measured the cellular contrast sensitivity of M4 ipRGCs we found that $Opn4^{-/-}$ M4 ipRGCs had significant deficits in contrast sensitivity at mean luminance levels ranging from scotopic (9 log quanta/cm^2/s) to photopic (12 log quanta/cm^2/s). These deficits were cell autonomous because we could acutely rescue contrast sensitivity deficits in $Opn4^{-/-}$ M4 cells that were virally infected with AAV2-hSyn-DIO-hM3D(Gq DREADD)-mCherry and exposed to bath application of 10 nM clozapine N-oxide (CNO) to activate the Gq pathway *in vitro*. Furthermore, we find that melanopsin phototransduction in M4 ipRGCs maintains a depolarized resting membrane potential at or above spike threshold for the cells and increases cellular excitability at all light levels tested. Combined, these influences of melanopsin phototransduction serve to optimize the response of M4 ipRGCs to the small, synaptic currents that would be associated with low

contrast stimuli, thereby enhancing the contrast sensitivity of M4 ipRGCs. These findings also allow us to link an observed behavioral influence of melanopsin phototransduction to a defined retinal cell population, the M4 ipRGCs.

Disclosures: **T.M. Schmidt:** None. **T. Sonoda:** None. **S. Lee:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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National Basic Research Program of China (973 Program, 2014CB542205, LZ)

National Natural Science Foundation of China 81470656

Title: The role of Celsr3 in the development of retinal starburst amacrine cells

Authors: ***X. XIAO**, N. SHEN, Y. XU, L. ZHOU
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Abstract: *Celsr3*, a core member of planar cell polarity (PCP) genes, encodes a seven transmembrane atypical cadherin and steers axonal projections in the different regions of the central nervous system during mouse brain development. In other species, *Celsr3* and its homologues (i.e. *Flamingo*) are required for visual development. For example, *Flamingo* regulated the organization of omatidium in *Drosophila*, and *Celsr3* mutation in zebrafish led to disrupted GABAergic signaling, which resulted in abnormal light response and visual function deficits. However, the role of *Celsr3* in mouse retinal development remains elusive. Here using *Celsr3-GFP* mice, we first found that *Celsr3* is expressed in some subtypes of amacrine cells and ganglion cells, as well as all horizontal, but not in photoreceptors or bipolar cells in adult retina. And during development, *Celsr3* keeps high expression in starburst amacrine cells (SACs) from P0 to P28. Then we conditionally inactivated *Celsr3* in SACs by crossing *Celsr3* "floxed" mice with *ChAT-Cre* mice. In *ChAT-Cre;Celsr3*$^{f/-}$ mice, mosaic spacing of ON- but not OFF-SACs is compromised. Moreover, ON- and OFF-SAC neurites fail to separate into two distinct bands in the inner plexiform layer with tangles and crosses in *ChAT-Cre;Celsr3*$^{f/-}$ retina, which emerges as early as P4. However, there are no significant defects in planar neurites arborization of SACs lacking *Celsr3*, implying that self-avoidance remains intact upon *Celsr3* knock-out. These results suggest that *Celsr3* shapes SAC development by regulating their planar soma distribution and neurites stratification, which provide a new insight into the role of *Celsr3* in neuronal circuits

assembly.
Key words: *Celsr3*; Starburst amacrine cells; Mosaic spacing; Neurites stratification; Retinal development.

Disclosures: **X. Xiao:** None. **N. Shen:** None. **Y. Xu:** None. **L. Zhou:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Sloan Fellowship

E. Matilda Ziegler Foundation Grant

McKnight Scholar Award

Title: Multiple synaptic mechanisms underlie global and object motion detection in the mammalian retina

Authors: X. HUANG[1], *W. WEI[2]
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Abstract: In mammalian retina, the direction-selective ganglion cells (DSGCs) encode the direction of image motion. DSGCs receive glutamatergic excitatory inputs from bipolar cell terminals and cholinergic excitatory inputs from starburst amacrine cells (SACs). The inhibitory inputs onto DSGCs come from SACs, which are asymmetrically wired with DSGCs to provide directionally tuned inhibition. Previous studies using conventional motion stimuli including moving bars and drifting gratings have revealed a set of key mechanisms underlying direction selectivity of DSGCs. However, the synaptic circuitry that is engaged during more complex motion stimuli is not well understood. In this study, we aim to determine the synaptic components that are involved in computing direction selectivity during global and object motion in the mouse retina. Using two-photon targeted patch-clamp recording of GFP-positive neurons for light response, we find that different patterns of background motion evoke differential suppression effects on DSGC response to motion within the receptive field center. The suppression is strongest when uniform motion stimuli are presented to the background and the center (global motion). To address the mechanisms underlying the differential suppression effects, we applied two types of SAC-targeted genetic manipulations. The first one perturbed GABA release from the SAC by conditionally knocking out the vesicular GABA transporter

(Vgat) gene in SACs; the other one blocked all GABAergic inputs onto SACs by removing their GABA receptors. By comparing DSGC response in these conditional knock-out mice, we find that distinct sets of synaptic connections contribute to the spiking response of DSGCs during global and object motion.

Disclosures: **X. Huang:** None. **W. Wei:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Brinson Foundation Award

Title: Lateral inhibition mediates excitation-inhibition covariation in retina direction selective circuit

Authors: *Q. CHEN, W. WEI
Univ. of Chicago, Chicago, IL

Abstract: Starburst Amacrine Cells (SACs) play an indispensable role in retinal motion computation by providing tuned excitatory and inhibitory inputs onto direction selective retinal ganglion cells (DSGCs). SACs receive GABA-A receptor-mediated inhibition from neighboring SACs and wide field amacrine cells. We have previously shown that this lateral inhibition is required for robust direction selectivity in noisy background for the On pathway. However, the mechanism underlying this function of lateral inhibition is not fully understood. Since the directional spiking pattern of DSGCs relies on the cancellation of excitation by inhibition in non-preferred directions, we hypothesize that the lateral inhibition onto SACs mediates the interaction of excitatory and inhibitory inputs onto DSGCs. To test this hypothesis, we performed voltage clamp recording of IPSCs and EPSCs in On-Off DSGCs both simultaneously and non-simutaneously, while stimulating the retina with a moving bar in the presence of random flickering noise. We then compared the difference of PSCs between control mice and mice that

lacks *Gabra2* (*Gabra2* KO) in SACs, a conditional knockout line previously developed to selectively remove lateral inhibition onto SACs. We find that disrupting lateral inhibition does not alter the directional tuning of IPSCs and EPSCs onto DSGCs, as measured by peak amplitude and charge transfer. However, in *Gabra2* KO mice, covariation between excitation and inhibition is significantly reduced in the null direction. This reduction of noise correlation in null direction is consistent with an increase in null-direction spiking in Gabra2 KO mice, revealed by loose patch recordings from DSGCs. Therefore, our results suggest that lateral inhibition onto SACs mediates the fine-scale balance of excitatory and inhibitory inputs onto On-Off DSGCs.

Disclosures: Q. Chen: None. **W. Wei:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Topic: D.07. Vision

Support: NRF Grant 2016R1D1A1A09918427

Title: Melanopsin-containing intrinsically photosensitive retinal ganglion cells are highly expressed in the noctural animal bat

Authors: M.-J. JEONG, H.-G. KIM, E.-B. PARK, *C.-J. JEON
Kyungpook Nat'l Univ., Daegu, Korea, Republic of

Abstract: Intrinsically photosensitive retinal ganglion cells (ipRGCs) respond to light and are involved in non-image forming vision such as circadian rhythms, pupil responses, regulation of sleep or image forming vision such as processing visual information and directing eye movements in response to visual clues. The purpose of this study was to identify the distribution, types and proportion of melanopsin-immunoreactive (IR) cells in nocturnal microbat retina. Three types of melanopsin-IR cells were found in the present study. M1 type had dendritic arbors extended into the OFF sublamina of the inner plexiform layer (IPL). M1 soma locations were observed either in the ganglion cell layer (GCL) (M1c; 21.00%) or the inner nuclear layer (INL) (M1d; 5.15%). M2 type had monostratified dendrites in the ON sublamina of the IPL and cell body in the GCL (M2; 5.79%). M3 type was bistratified cells with dendrites in both the ON and OFF sublaminas of the IPL and soma locations were either in the GCL (M3c; 26.66%) or the INL (M3d; 4.69%). In this study, some M3c (M3c-crv) had a curved dendrite heading up to the OFF sublamina of the IPL and heading down to the ON sublamina of the IPL (M3c-crv; 7.67%). Melanopsin-IR cells had small to medium soma size and medium dendritic fields. They had 2-5 primary dendrites and sparsely branched dendrites with varicosities. The total number of the

neurons in the GCL was 12,254.17 ± 660.39 (mean ± S.D.; n = 3) and that of the optic nerve axons was 5,179.04 ± 207.99 (mean ± S.D.; n = 3) in the bat retina. The density of melanopsin-IR cells was 227.12 ± 11.41 cells/mm^2 (mean ± S.D.; n = 4) and it was estimated that ipRGCs constituted about 15.83% of total RGC population. The study shows that the nocturnal bat has much higher density of melanopsin-IR cells than diurnal animals studied so far.

Disclosures: **M. Jeong:** 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.; This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by Ministry of Education (NRF-2016R1D1A1A09918427).. **H. Kim:** None. **E. Park:** None. **C. Jeon:** 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.; This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by Ministry of Education (NRF-2016R1D1A1A09918427)..

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Topic: D.07. Vision

Support: NRF Grant 2016R1D1A1A09918427

Title: Cholinergic neurons in the bat retina: Different dendritic stratification pattern as compared to other animals

Authors: *E.-B. PARK[1,2,3,4], J.-Y. JEON[1,2,3,4], G.-H. KIM[1,2,3,4], M.-J. KWON[1,2,3,4], E.-S. LEE[1,2,3,4], C.-J. JEON[1,2,3,4]
[1]Sch. of Life Sci., [2]BK21 Plus KNU Creative BioResearch Group, [3]Col. of Natural Sci., [4]Brain Sci. and Engin. Inst., Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: The purpose of this study was to localize the cholinergic amacrine cells, one of the key elements of a functional retina, in the retina of a microbat, *Rhinolophus ferrumequinum*. The presence and localization of choline acetyltransferase-immunoreactive (ChAT-IR) cells in the microbat retina were investigated using immunocytochemistry, confocal microscopy, and quantitative analysis. These ChAT-IR cells were present in the ganglion cell layer (GCL) and inner part of the inner nuclear layer (INL), as previously reported in various animals. However, the bat retina also contained some ChAT-IR cells in the outer part of the INL. The dendrites of these cells extended into the outer plexiform layer, and those of the cells in the inner INL

extended within the outer part of the inner plexiform layer (IPL). The dendrites of the ChAT-IR cells in the GCL extended into the middle of the IPL and some fibers ramified up to the outer IPL. The density of ChAT-IR cells was highest in the mid-ventral and mid-temporal retina. The average densities of ChAT-IR cells in the GCL, inner INL, and outer INL were 259 ± 31 cells/mm^2, 469 ± 48 cells/mm^2, and 59 ± 8 cells/mm^2, respectively. The average total density of the ChAT-IR cells was 788 ± 58 cells/mm^2 (mean ± S.D.; n = 3; 2,799 ± 182 cells/retina). We also found that the cholinergic amacrine cells in the bat retina contained calbindin, one of the calcium-binding proteins, but not calretinin or parvalbumin. As the cholinergic amacrine cells play key roles in the direction selectivity and optokinetic eye reflex in the other mammalian retinas, the present study might provide better information of the cytoarchitecture of bat retina and the basic sources for further physiological studies.

Disclosures: E. Park: None. **J. Jeon:** None. **G. Kim:** None. **M. Kwon:** None. **E. Lee:** None. **C. Jeon:** 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.; This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by Ministry of Education (NRF-2016R1D1A1A09918427)..

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Topic: D.07. Vision

Support: National Natural Science Foundation of China (81470656)

Title: Inhibition of Non-NMDA ionotropic glutamate receptors delays retinal degeneration in rd10 mice

Authors: Z. XIANG, J. ZHANG, *Y. XU
Jinan Univ., Guangdong, China

Abstract: Purpose: Retinitis pigmentosa is a progressive neurodegenerative disease that cause deterioration of rod and cone photoreceptors and is the leading cause of blindness in the world. The aim of this study is to understand the progress of the disease focusing in the glutamate pathway, and to seek effective way to protect the function of retinal neurons, hoping to provide a new strategy to treat retinitis pigmentosa in the clinic. **Methods:** In our study, we used rd10 mice, a well-established animal model of retinitis pigmentosa, to detect the changes of glutamate receptors expression during photoreceptor degeneration and the impact on the functions of retinal ganglion cells. We firstly checked the changes of ON signal cascade proteins (metabotropic

glutamate receptor 6, mGluR6 and TRPM1 proteins) and OFF signal cascade related ionotropic glutamate receptors(iGluRs)by immunostaining. Then we used multi-electrode-array (MEA) system to record the light response of ganglion cells and the effects of perfusing low dose of CNQX (non-NMDA iGluRs antagonist) on the functions of retinal ganglion cells. Lastly, we i.p. injected rd10 mice with CNQX for 2 weeks, and examined the changes of light response of ganglion cells and the morphology of retinal neurons, as well as the animal behavior. **Results:** mGluR6 and TRPM1 were down-regulated in the outer plexiform layer during photoreceptors degeneration. In contrast, iGluRs were up-regulated in the inner plexiform layer, and AMPA receptors formed abnormal clusters in the outer plexiform layer. During photoreceptors degeneration, the light response of ganglion cells in rd10 retina decreased while the spontaneous spiking increased abnormally. Both in vitro and in vivo application of low-dose CNQX inhibited the abnormal spontaneous spiking and increased the light evoked response of ganglion cells. Furthermore, in vivo application of CNQX increased the survival of photoreceptors, improved the morphology of bipolar cells as well as the behavioral performance. **Conclusion:** Our data indicate that blocking the ionotropic glutamate signal pathway by CNQX delays the functional decay of ganglion cells during photoreceptors degeneration, thus it might be an effective strategy to prolong the time window for the treatment of retinitis pigmentosa.

Disclosures: Z. Xiang: None. **J. Zhang:** None. **Y. Xu:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Program#/Poster#: 684.26/GG7

Topic: D.07. Vision

Title: Differential expression and sub cellular localization of copines in mouse retina

Authors: *M. GOEL, ***M. GOEL**, T. LI, T. C. BADEA
Natl. Eye Inst., NIH, Bethesda, MD

Abstract: Brn3 transcription factors are important for cell type specific arbor formation and dendrite stratification in the retina. Brn3b might be regulating several downstream genes that have a role in cell specific dendritic stratification and synapse formation in the inner retina. From the RNA sequencing done previously in our lab on wild -type and Brn3b $^{-/-}$ mouse retinas (Sajgo et al., 2017), we identified a family of proteins - Copines - which are regulated by the Brn3b transcription factor. There are nine Copines (1 to 9) present in the mammalian genome. Copines are intracellular, membrane bound proteins containing two C2 domains and an integrin-like von Willebrand A domain. Recently, Cpne6 has been shown to be important for synaptic plasticity and LTP formation in the hippocampus (Reinhard et al., 2016; Burk et al., 2017). Hence, the Copines might have a role in synapse formation in the Inner Plexiform Layer (IPL) in retina.

The aim of this study was to study the expression profile of the Copines in post-natal retina. We studied the expression of the Copine mRNAs in P0, P3, P7, P14 and adult retinas using in-situ hybridization. We also checked the expression of the Copine proteins using immunohistochemistry (IHC) in adult retina. To study the sub cellular distribution, HEK293 cells were transfected with the HA tagged Copines. Sub cellular distribution of Copines in the $Brn3b^+$ Retinal Ganglion Cells was also studied in virus infected retinas.
Copine proteins are expressed in the retina starting from early postnatal ages and have a dynamic expression through retinal development. The different copines have a differential expression pattern in the RGCs and amacrine cells. The HEK 293 cells transfected with Copines and Cre dependent expression of Copine in Brn3b RGCs indicated the expression of Copine in the nuclei, cell bodies as well as the dendrites of the cells. Moreover, a lot of the transfected HEK293 cells had 'neurite-like' processes.
The differential expression of different Copines suggests that they might be providing a combinatorial code for cell type specific dendritic stratification and synapse formation in the inner retina.

Disclosures: M. Goel: None. **T. Li:** None. **T.C. Badea:** None.

Poster

684. Retina: Inner Circuits and Ganglion Cells

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Topic: D.07. Vision

Title: Inner retinal contributions shape the b-wave of the electroretinogram (ERG) in adult zebrafish

Authors: A. HERRERA, *S. SASZIK
Psychology, Northeastern Illinois Univ., Chicago, IL

Abstract: Purpose: The electroretinogram (ERG) is mass retinal potential that can be recorded with an electrode on the cornea. Contributions from outer retinal neurons have been well described, however recent research has identified contributions from inner retinal neurons in some mammalian species. The purpose of the current experiments is to determine if contributions from ganglion cells can be identified in the light-adapted ERG in zebrafish.
Methods: To determine ganglion cell contributions to the ERG were recorded in control (CON) conditions and one week post optic nerve crush (ONC). Adult zebrafish were anesthetized and the eye rolled slightly to expose the optic nerve. The nerve was then crushed with forceps for 3 seconds. The fish was then placed into a 2.5 gallon tank and allowed to recover. After one week, fish were again anesthetized and electroretinograms (ERGs) recorded to a 50 ms flash of monochromatic light under light adapted conditions. Four wavelengths were tested (340 nm, 420

nm, 520 nm, and 620 nm). The amplitude of each response was measured at 180 ms. Intensity response function were plotted and comparisons of amplitude, time to peak, and threshold were measured.
Results: Examination of the ERG responses found no difference based on the wavelength of the light, thus data from the individual wavelengths was compiled and comparisons were made for CON and ONC. After ONC there was an increase in the time to peak (CON M=221.6 ms, SEM=1.9; ONC M=236.3 ms, SEM=6.9) and a decrease in the peak amplitude of the b-wave (CON M=1041.3 microvolt, SEM=98.1; ONC M=840.5 microvolt, SEM=102.6). Additionally, a ssignificant increase was found in the 50 microvolt threshold (CON M=6.3 log photons, SEM=0.1; ONC M=6.7 log photons, SEM=0.1). Further examination showed that in addition to a loss at 180 ms, a negative potential that has a time to peak around 300 ms was also removed.
Conclusion: After ONC several changes were seen in the ERG response that had an impact on the time course and amplitude of the b-wave suggesting the presence of a contribution reflecting the activity of ganglion cells. The loss of a negative potential after the b-wave is suggest that the zebrafish also has a photopic negative response. Together these results will provide some information about the cellular contributions to the ERG in zebrafish.

Disclosures: **A. Herrera:** None. **S. Saszik:** None.

Poster

685. Motion: Psychophysics

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Topic: D.07. Vision

Support: This research was supported by the Scientific and Technological Research Council of Turkey (TUBITAK Grant 215S701)

Title: Motion direction discrimination during neural aging

Authors: A. KARADUMAN[1,2], U. KAYA[1,5], E. T. KAROGLU[2,3], A. ERGUL-ARSLAN[2,3], M. M. ADAMS[2,3,4], *H. KAFALIGONUL[1,2]
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Abstract: Understanding the principles underlying age-related changes in perception and cognition is paramount to improve the quality of life and health of elderly individuals. A number of studies have shown that the perception of visual motion is significantly altered throughout aging (Owsley, 2011). However, the neural mechanisms underlying the effect of aging on this aspect of vision, which is essential for survival in a dynamic world, are quite poorly understood.

The zebrafish have been commonly used as an aging model (Arslan-Ergul et al., 2013). Moreover, several studies have shown that zebrafish perceive first-order (Fourier) and second-order (non-Fourier) motions, suggesting that they have very similar motion systems as in humans (Orger et al., 2000). Using this animal model which offers a framework not only for aging but also for visual motion perception, we aimed to characterize contrast and spatial frequency dependency of direction discrimination for young (AB wild-type, 8-10 months) and old (AB wild-type, 24-30 months) groups. In our experiments, we used first-order and second-order drifting gratings, and relied on the averaged and normalized optomotor responses to these motion types. To generate the first-order motion, we used sine-wave gratings with varying contrasts (1-75 %) and spatial frequencies (0.01-0.8 c/deg). The second-order motion consisted of random dots and was flicker-frequency-modulated. The flicker frequency of the static random dots was modulated by a drifting square-wave (half-wave rectified, 50% duty cycle). We used the same spatial frequency values (0.01-0.8 c/deg) for the second-order motion. Our results showed that the optomotor responses were affected by the contrast and spatial frequency of first-order motion. However, these effects were distinct for each zebrafish group. Interestingly, compared to the young ones, the old zebrafish had larger optomotor response to the first-order motion with low contrast and spatial frequency, suggesting that they discriminate the direction of first-order motion better at the threshold level. On the other hand, the young group generated larger optomotor responses to second-order motion than the old group. Taken together, our findings here highlight distinct effects of aging on the first-order and second-order motion which are mostly believed to engage different motion systems. Characterizing these motion types for mutants in which the aging is accelerated or decelerated awaits further investigation.

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Poster

685. Motion: Psychophysics

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Topic: D.07. Vision

Support: Natural Science Foundation of China Grants (31571160) to S.K.

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Title: Neural mechanisms for integrating motion and form cues for the perception of heading during self-motion

Authors: *S. KUAI[1,2,3], Z.-X. XU[1,2], J. CHEN[3], J.-M. LI[1,2], D. T. FIELD[4], L. LI[3]
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Abstract: When moving around in the world, the human visual system uses both form and motion information to estimate the direction of self-motion (i.e., heading). However, the neural mechanism responsible for integrating motion and form cues for heading perception remains unknown. In this study, we explored the brain areas that process form cues for heading perception and examined whether they overlap with the known brain areas that process motion cues for heading perception. We further investigated brain areas responsible for integrating motion and form cues for heading perception. Specifically, we used integrated glass patterns that had dot pairs oriented toward a locus on a screen (the form-defined focus of expansion (FOE)) but moved away from a different locus (the motion-defined FOE). The form- and the motion-defined FOEs were congruent or incongruent. In the congruent condition, the form- and the motion-defined FOEs were centered on the same location on the screen. In the incongruent condition, the form- and the motion-defined FOEs were on the opposite side relative to the center of the screen. Different stimulus conditions were presented in separate blocks in fMRI scans. Participants made a task-irrelevant (luminance discrimination) judgment during scanning. We compared BOLD response patterns across stimulus conditions using multiple voxel pattern analysis. We selected the 200 most active voxels in each ROI, trained a linear SVM to discriminate stimulus types, and then tested the classifier's prediction for each stimulus block. We found that early visual areas (V1 and V2) decoded both the form- and the motion-defined FOEs but could not discriminate the congruent and incongruent conditions, suggesting that these areas do not integrate form and motion cues for heading perception. The higher ventral areas (V4 and LO) decoded the form- but not the motion-defined FOE while the dorsal areas (MT and MST) decoded the motion- but not the form-defined FOE. In contrast, the higher dorsal areas (V3a, V3B and V7) and the parietal lobe (VIP and CSV) not only decoded both the form- and the motion-defined FOEs but also dissociated the congruent and incongruent conditions, suggesting that they contribute to the integration of form and motion cues for heading perception. Our findings provide the first empirical evidence suggesting that form and motion information are first processed along separate pathways and then integrated in the higher dorsal areas for the final estimation of heading during self-motion.

Disclosures: S. Kuai: None. **Z. Xu:** None. **J. Chen:** None. **J. Li:** None. **D.T. Field:** None. **L. Li:** None.

Poster

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Topic: D.07. Vision

Support: NWO/MagW

CSC

Title: Reverse-phi motion: Optomotor reflexes and visual cortex responses for a visual illusion of motion in mice

Authors: L. KIRKELS[1], J. DUIJNHOUWER[2], W. ZHANG[1], M. N. HAVENITH[1], J. GLENNON[1], P. H. TIESINGA[3], *R. VAN WEZEL[4]
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Abstract: In reverse-phi motion, the contrast luminance of moving dots is reversed at each displacement step. Under those conditions their direction of motion is perceived as opposite to their veridical direction of displacement. In this study, we investigate whether mice also perceive a reverse-phi motion effect/illusion. In a virtual reality environment, mice were subjected to an immersive moving-dot stimulus that featured sudden changes in direction of regular motion (phi-motion) and reverse-phi motion. Mice were head-fixed and running on a floating-ball treadmill, surrounded by a projection dome covering 270 degrees of visual angle. For phi-motion, motion onsets to the left or right cause animals to reflexively compensate, adjusting their running direction towards the moving pattern. In contrast, for reverse-phi motion, mice compensate in the opposite direction, in accordance with the illusory motion that humans perceive for reverse-phi motion stimuli. We used two-photon calcium imaging to measure the neural responses of layer 2/3 primary visual cortex (V1) neurons of awake mice that passively viewed the moving dots on a screen. We find that only a small fraction of direction selective V1 neurons reverse their preferred direction for phi and reverse-phi motion, firing maximally at their null-direction. At the population level there was no statistically significant effect. The discrepancy between the clear behavioral impact of reverse-phi stimuli and their very moderate effect on V1 responses suggests that the illusion is processed via alternative visual pathways, e.g. superior colliculus, of which the individual cell responses during these stimuli were not measured in the current study.

Disclosures: L. Kirkels: None. **J. Duijnhouwer:** None. **W. Zhang:** None. **M.N. Havenith:** None. **J. Glennon:** None. **P.H. Tiesinga:** None. **R. Van Wezel:** None.

Poster

685. Motion: Psychophysics

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Program#/Poster#: 685.04/GG12

Topic: D.07. Vision

Title: Comparing objective measures of occulomotor insuficiencies

Authors: *D. L. LARRANAGA[1], J. F. AWAD[2], M. F. AWAD[3], D. A. DEL CID[6], T. GORJI[4], S. A. DREW[5]
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Abstract: Asthenopia is a condition characterized by significant visual discomfort symptoms including, but not limited to symptoms of blurred vision, double vision, and strained, sore, or tired eyes. In the past, self-report surveys have been used to assess the severity of asthenopic symptoms (e.g. the Visual Discomfort Survey, Conlon et al. 1999). In contrast to other works that have evaluated the effectiveness of such surveys, the present study aims to compare two different technologies used to obtain objective measures of oculomotor ability: a WAM-5500 autorefractor to evaluate accommodative posture, and Eyelink 1000 Plus eye-tracker to record multiple forms of oculomotor movements. Previous studies have examined similar phenomena using accommodative recordings to evaluate the effectiveness of surveys (i.e. Chase et al., 2009; Tosha et al., 2009). However, the present work aims to expound upon these findings through the use of two extended reading tasks on the computer; before and after each task, accommodative posture was evaluated via the autorefractor. The eye-tracker is likewise an additional tool that was used to collect data during one of the two reading task, and may be an indicator of convergence insufficiencies, which also have been shown to contribute to visual discomfort symptoms. Data from this preliminary study indicate multiple relationships observed between the accommodative postures, as recorded via the autorefractor, and oculomotor activity observed during eye-tracking. The use of objective laboratory techniques such as these, in conjunction with survey data, may help researchers with non-optometric evaluations of asthenopia. With the present dependency on computers in fields such as neuroscience, asthenopic symptoms induced by computer screens still need to be better understood before they can be mitigated.

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Poster

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Topic: D.07. Vision

Title: Light/dark asymmetries in motion perception

Authors: *A. W. FREEMAN, G. LUO-LI
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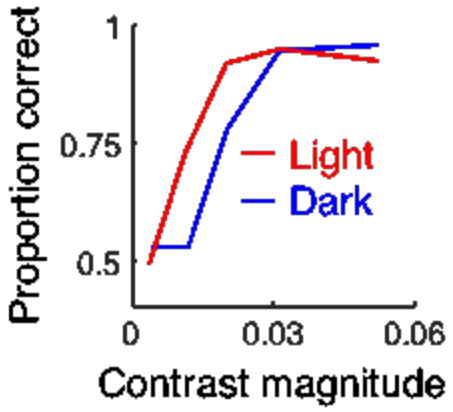
Abstract: Introduction. It is now well-established that responses to stationary light and dark stimuli of equal magnitude are asymmetric: psychophysical and neural responses to darks are larger and faster than responses to lights. We wondered whether this asymmetry might play a role in motion perception. We therefore measured the sensitivity of six human subjects to light and dark moving edges and bars. **Methods.** Stimuli were enveloped by a Gaussian spatial profile with a standard deviation of 0.3 deg, bar width was 0.1 deg and speed was 1, 3 or 10 deg/s. Movement was leftward or rightward, and the subject's task was to indicate motion direction. Stimulus contrast on each trial was sampled from a Gaussian probability density with zero mean, so that there was equal probability of a light or dark. We measured both the proportion of correct responses and reaction time. **Results.** We compiled psychometric and chronometric functions separately for light and dark stimuli: pooled psychometric data obtained with a bar moving at 3 deg/s are shown in the figure. Surprisingly, responses to light stimuli were stronger and faster than those to darks. At 3 deg/s the contrast sensitivity for lights (measured at the midpoint of the psychometric function) was 57% higher than for darks. At the same speed, reaction time for lights (measured at the midpoint of the chronometric function) was 32 ms less than for darks. The asymmetry was biggest at 1 deg/s and nearly absent at 10 deg/s. **Discussion.** Very high speeds will minimally stimulate motion-selective mechanisms and should appear to be stationary flashes. From previous work, we can therefore expect that responses to fast-moving dark stimuli will dominate those to lights; the trend we measured was in this direction. Why do lights dominate darks at low speeds? One possibility is the effect of surround suppression. Primary visual cortex is, in general, dark-dominated and a dark moving stimulus will generate more surround suppression that a light one. Perhaps, then, responses to dark moving stimuli are suppressed more that their light-evoked counterparts. We are testing this idea.



Disclosures: **A.W. Freeman:** None. **G. Luo-Li:** None.

Poster

685. Motion: Psychophysics

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Topic: D.07. Vision

Support: This work was supported by the Roskamp Foundation

Title: Assessment of visual dysfunction of the optomotor response in APOE transgenic mice after TBI

Authors: *S. FERGUSON[1], T. SMITH[1], B. C. MOUZON[2], D. APONTE[1], M. J. MULLAN[1], F. C. CRAWFORD[1]
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Abstract: Our mouse model of repetitive mild TBI (r-mTBI) produces chronic optic nerve pathology and retinal degeneration. The APOE4 allele has previously been shown to be associated with poor outcome after head injury. In order to assess the visual function of APOE transgenic mice, we have optimized a mechanical assay to assess the optomotor response. The optomotor apparatus consisted of a rotating drum containing black and white stripes at varying angular resolutions at 2 rpm. Mice were acclimated to the apparatus for a period of 5 minutes in phototopic lighting. Optomotor testing at each resolution consisted of pairs of 2 minute trials with 1 trial in a clockwise rotation followed by 1 trial in a counter-clockwise rotation with an inter-trial time of 30 seconds. After the completion of all 4 trials the mouse was returned to the home cage and the next mouse was tested. All trials were recorded with Noldus Ethovision XT using both manual and automatic quantification. Optomotor testing and optimization revealed a quantifiable optokinetic response of the mice which decreased with decreasing stripe thickness,

and was significantly impaired in APOE4 transgenic mice after TBI. Ethovision XT based quantification of the head velocity failed to show a stripe-dependent decrease of the optomotor response, but more advanced pattern recognition algorithms may allow for more accurate automated detection of the optomotor response in the future. By varying the resolution of the stripes we were able to increase the difficulty of the task and determine the optimal conditions for discriminating subtle vision deficits. APOE4 transgenic mice show a significant vision impairment compared to sham controls, but current commonly used animal tracking software is insufficient for discriminating between the optomotor response and random head movements.

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Poster

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Topic: D.07. Vision

Support: NIH 1T32 EY021462

NIH R01 EY05729

Title: Optic flow and visual self-motion information during real-world locomotion

Authors: *J. S. MATTHIS[1], K. S. MULLER[2], N. K. SCHNEIDER[3], K. BONNEN[1], M. M. HAYHOE[1]
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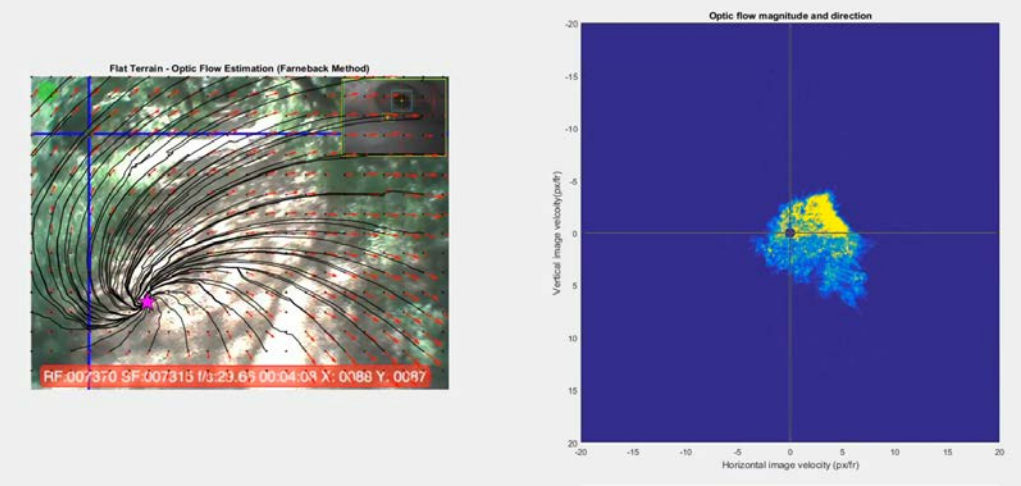
Abstract: A large body of research has examined the way that patterns of motion on the retina might contribute to perception of self-movement through the world, but the actual visual motion stimulus generated by real-world locomotion has never been measured. We used computer vision techniques to estimate optic flow from a head-mounted video camera, recorded when subjects walked over various types of real-world terrain. Eye, head, and body movements were also recorded. We found that the optic flow experienced during locomotion reveals a pulsing pattern of visual motion that is coupled to the phasic acceleration patterns of the gait cycle, unlike the constant-velocity flow fields that are generally used to simulate self-motion. This difference between actual and simulated visual self-motion has a major effect on the behavior of the focus of expansion (FOE), a feature of optic flow that has been extensively studied as a locus of information about heading direction, but one that has not previously been recorded during natural behavior. Results show that the acceleration patterns of the head cause the FOE to follow a

complex path in the visual field, in contrast to simulated constant-velocity self-motion stimuli, where the FOE lies in a stable location in observer's environment. Thus its role in the control of heading must be more complex than previously imagined. Although the behavior of the FOE and the self-motion information experienced during locomotion are complex, their dynamics contain rich and potentially useful structure for the control of locomotion and posture.



Disclosures: **J.S. Matthis:** None. **K.S. Muller:** None. **N.K. Schneider:** None. **K. Bonnen:** None. **M.M. Hayhoe:** None.

Poster

685. Motion: Psychophysics

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Topic: D.07. Vision

Title: Optomotor reflexes of mice to moving random dot patterns at different speed, contrast and dot-size

Authors: *W. ZHANG[1], L. KIRKELS[2], J. DUIJNHOUWER[3], M. N. HAVENITH[2], P. H. TIESINGA[4], J. GLENNON[5], R. VAN WEZEL[6]
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Abstract: A frequently used method to measure visual capabilities of mice is to observe reflexive head movements to moving patterns. In this study we introduce another technique that

also does not require training, but is more quantitative by recording traces of mice running head-fixed on an air-floated ball, while projecting large moving random dot patterns on the inside of a dome. Sudden onset of rightward or leftward moving patterns caused reflexive changes in the mouse running direction. We used these optomotor reflexes to quantify visual responses for different pattern speed, luminance contrast and dot size. The strongest reflexes are evoked with pattern speeds between 36 and 72 degrees per second, a luminance contrast of 0.2 and a dot size of 2 degrees, with an additional interaction effect between speed and luminance. Results revealed that changes in both contrast and dot size affect speed sensitivity . Furthermore, the obstruction of the left or right eye leads to stronger optomotor reflexes for leftward or rightward motion respectively. Our paradigm is a fast, consistent and a reliable test of optomotor response, with no adaptation effects within or across sessions. Most importantly, it does not require task training while at the same time testing more than purely reflexive visuo-motor responses. We conclude that this method is suitable for studies that need a fast and quantitative description of visually guided behavior in mice.

Disclosures: W. Zhang: None. **L. Kirkels:** None. **J. Duijnhouwer:** None. **M.N. Havenith:** None. **P.H. Tiesinga:** None. **J. Glennon:** None. **R. Van Wezel:** None.

Poster

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Support: DFG-IRTG-1901-The Brain in Action

NSERC Discovery grant

Title: TMS-induced disturbance of self-motion perception in humans

Authors: *C. SCHMITT[1], B.-R. BALTARETU[2], J. D. CRAWFORD[2], F. BREMMER[1]
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Abstract: Accurate perception of one’s direction of self-motion is of utmost importance during everyday life. Previous neurophysiological studies in the animal model (macaque monkey) and imaging studies in humans have provided clear evidence for an involvement of area MST in the encoding of self-motion. In a recent study combining monkey neurophysiology, human psychophysics and computational modeling we could show that saccadic eye movements modulate heading representation. The computational part of our study predicted a direction specific TMS-induced increase of response variance of heading perception. Here we wanted to investigate by means of neuronavigated transcranial magnetic stimulation (TMS) if (i) TMS can

mimic the effects of saccades on heading perception and if (ii) TMS indeed induces a greater variance of heading perception for simulated self-motion contraversive to the TMS stimulation site.
We presented an optic flow stimulus (random dot pattern) on a large projection screen 54 cm in front of the participants. In a given trial, the stimulus first was stationary, then moved for 50 ms, simulating forward self-motion across a ground plane in one of three directions separated by 30°, and was stationary again. Participants fixated a central target throughout the trial. After each trial, participants had to indicate perceived heading direction. In 57% of the trials three TMS pulses were applied, separated by 100 ms each, centered on self-motion onset. TMS-stimulation site was either right-hemisphere MST, which we identified using an fMRI localizer, or a control area 1.5 cm posterior to human MST.
TMS over MST increased response variance of perceived heading. Remarkably, and as predicted by our model, this result was strongest for simulated self-motion to the left (contraversive). This contraversive specificity was absent from the TMS control area. Different to saccades, which induce a compression of perceived heading, TMS pulses induced misperception towards both, more central and more peripheral, headings. Our results provide further evidence for a critical role of primate area MST for navigation.

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Poster

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Topic: D.07. Vision

Support: EY000404

Title: Short-latency ocular responses are strongly affected by the visual content during the initial fixation period

Authors: *B. M. SHELIGA, C. QUAIA, E. J. FITZGIBBON, B. G. CUMMING
Lab. Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

Abstract: We recorded horizontal disparity-vergence responses (DVRs) to vertical 1D pink noise in two human subjects. The stimulus was preceded by 800-1100 ms of maintained fixation (on a visible cross), and we explored the effect of different stimuli (“fixation patterns”) presented during the fixation period. When the fixation pattern was a blank screen, the DVR usually had two well-defined peaks of acceleration—early and late. When the fixation pattern was a different sample of static zero-disparity noise, the early component was absent, resulting in weaker

responses with longer latency. When the fixation pattern was a dynamic noise stimulus at zero disparity the DVR latencies were even longer, and response magnitudes peaked at smaller disparities than those obtained with blank or static fixation patterns. When the dynamic noise stimuli were binocularly uncorrelated during the fixation period, we observed a still further drop (up to 60-70%) in the DVR amplitude. We found a different pattern using motion stimulus to drive short-latency ocular-following responses (OFRs). Blank and static fixation patterns produced similar responses. A flickering fixation pattern led to a massive drop in the OFR amplitude, very much like we observed with the DVRs when the fixation period images were uncorrelated in the two eyes. Thus, the visual context preceding the stimuli triggering the DVRs (as well as the OFRs) exerts a dramatic influence upon the characteristics of these short-latency ocular responses. These interactions can be explained by suggesting that transient and sustained visual inputs both contribute, but drive mechanisms with different disparity (or motion) responses. For example, the appearance of a stimulus following a blank screen activates transient channels. If these produce responses with shorter latency, it explains the changes in latency we observe. Some aspects of the measured response with blank fixation patterns may reflect the properties (e.g. spatial frequency tuning) of mechanisms driven by sudden contrast changes. For DVRs, only the dynamic fixation pattern isolates purely binocular processing - in this condition the appearance of the disparity driving the DVR is not associated with any monocular changes.

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Poster

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Topic: D.07. Vision

Support: NIH F32 EY025121 to MPS

NIH R01 MH106520 to SOM

NIH T32 EY007031

Title: Suppression and facilitation of neural responses in the human visual system

Authors: *M.-P. SCHALLMO, A. M. KALE, R. MILLIN, A. V. FLEVARIS, R. A. BERNIER, S. O. MURRAY
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Abstract: Neural suppression and facilitation regulate levels of activity within the brain, but how these effects are mediated remains poorly understood. Both reduced and enhanced neural

responses are well-known to emerge in the visual system via spatial context effects, and have a variety of perceptual consequences. For example, the perception of visual motion has been reliably shown to depend on the size and contrast of a stimulus. Specifically, more time is needed to discriminate the direction of motion of a large high contrast grating compared to one that is small. This seemingly paradoxical effect is referred to as spatial suppression, and has been suggested to reflect neural suppression from extra-classical receptive field surrounds. The effect of size on duration thresholds is reversed for a low contrast stimulus - less time is needed to discriminate motion direction for a large compared to small stimulus (spatial summation). Strong assumptions are often made about the neural processes underlying these seemingly complex interactions between size and contrast during motion perception. For example, it is often assumed that spatial suppression and summation reflect distinct neural mechanisms that rely on inhibitory and excitatory processes, respectively, within brain regions involved in visual motion processing (particularly area MT).
We tested these assumptions directly using a multi-modal approach that combined five different techniques: functional MRI (fMRI), magnetic resonance spectroscopy (MRS), pharmacology, quantitative behavioral analysis (psychophysics), and computational modeling. We show that: 1) spatial suppression and summation in fact naturally emerge from a single, well-established neural computation known to occur in visual cortex - divisive normalization; there is no need to posit separate mechanisms. 2) While neural responses in human MT complex (hMT+) indexed with fMRI provide better correspondence with the measured perceptual effect, there is substantial suppression in earlier visual areas. 3) Two separate methodologies - magnetic resonance spectroscopy (MRS) and pharmacological potentiation of $GABA_A$ receptors - demonstrate that spatial suppression is not directly linked to neural inhibition. While we find that inhibition plays a role in motion perception, increases in duration threshold as a function of stimulus size should not be taken as an index of inhibitory processing. In total, our results suggest that a single computational principle - divisive normalization - can account for spatial context effects, and that suppressive context effects are not driven by neural inhibition.

Disclosures: **M. Schallmo:** None. **A.M. Kale:** None. **R. Millin:** None. **A.V. Flevaris:** None. **R.A. Bernier:** None. **S.O. Murray:** None.

Poster

685. Motion: Psychophysics

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Program#/Poster#: 685.12/GG20

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI (21300125, 25280051, 26119519,16H01510)

Title: A study of direction discrimination task using a touchscreen method in rats

Authors: *S. SAKATA[1], Y. IIO[2], Y. NAKAMURA[2]
[2]Dept. of Behavioral Sci., [1]Hiroshima Univ., Hiroshima, Japan

Abstract: Motion lines (MLs) are an effective technique for illustrating dynamic events such as fast movement of an object in a still picture. Perception of moving objects correlate with timing ability. This study explored whether MLs have the same effect for human and animals. First, we had a task to discriminate the motion direction of circles using touchscreen method in rats. Six male Long-Evans rats were food restricted and trained to perform moving visual tasks for food reinforcement. Animals were trained to perform two alternative left and right side operant choice visual discrimination of the direction of the motion. The discrimination moving stimuli were presented with five white circles background in dark display. All six rats showed good performance of direction discrimination over 80 % correct responses in forty training sessions. Then we tested with five kinds of MLs probe stimulus. These probe stimuli were 1) apparent movement five circles with MLs in low flame rate, 2) five circles with MLs at random position, 3) MLs with one side in a still picture, 4) MLs with both side in a still picture, 5) only five circles without movement. The results showed that its performance in MLs probe in a still picture were chance level. But in apparent movement probe showed good performance like motion direction discrimination. These results of this study suggest that rats could visual discriminate in apparent movement stimuli like human visual performance.

Disclosures: S. Sakata: None. **Y. Iio:** None. **Y. Nakamura:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.01/GG21

Topic: D.10. Multisensory Integration

Support: NSF IOS 1354932

Title: Encoding multisensory information through distinct population activity in a premotor region

Authors: *C. J. GOLDSMITH, R. FOLLMANN, W. STEIN
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Abstract: Integrating information from multiple sensory modalities and producing appropriate motor outputs are vital functions of the nervous system, and the neural networks underlying these two functions are tightly linked. Most motor circuits produce a variety of distinct outputs in different sensory conditions (Li et al., *J Neurosci* 2016), yet it remains ambiguous how this is achieved by the nervous system. While traditionally not considered multisensory, premotor

circuits in both vertebrates and invertebrates are known to process information from several sensory modalities. In the crustacean stomatogastric nervous system, several neurons in the premotor region of the commissural ganglion are activated by multiple sensory pathways and modulate downstream motor circuits (CoGs; Stein, *J Comp Physiol A* 2009). Stimulation of individual premotor neurons can elicit distinct versions of the gastric mill motor pattern (Nusbaum & Beenhakker, *Nature* 2002), though it is likely that in conditions of natural behavior, several of these neurons are recruited simultaneously. We hypothesize that distinct combinations of neuronal recruitment in the CoG premotor region exist across different sensory conditions, i.e. multisensory information is processed via a combinatorial code.
We used selective stimulation of a chemosensory (inferior ventricular neurons, IV) and a mechanosensory (ventral cardiac neurons, VCN) pathway in combination with voltage-sensitive dye imaging to characterize the CoG neuronal network response under different sensory conditions. We show that both pathways activate the majority of imaged neurons, resulting in an overlapping (~80% multimodal neurons), yet consistently distinct (~20% unimodal neurons) network response between the two conditions (N=12 animals). In particular, VCN stimulation led to a higher proportion of excited neurons, while IV stimulation yielded a higher proportion of inhibited neurons in the premotor region. The specific neurons contributing to the network response were also distinct between inputs. Moreover, concurrent stimulation of IV and VCN pathways resulted in a network response that was not the additive result of the two unisensory conditions (N=6 animals). Our findings thus suggest that: (1) premotor neuronal networks distinctly encode different sensory inputs, and (2) there is an additional network reconfiguration in response to concurrent stimulation.

Disclosures: C.J. Goldsmith: None. **R. Follmann:** None. **W. Stein:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.02/GG22

Topic: D.10. Multisensory Integration

Support: The Gatsby Charitable Foundation

Title: Efficient coding of multisensory or multi-modality inputs by congruent and opposite neurons

Authors: *L. ZHAOPING
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Abstract: Many medial superior temporal (MST) neurons are tuned to heading direction of self-motion based on optic flow or vestibular inputs. The preferred directions from different senses

within a single neuron can be congruent (matched) or opposite from each other (Gu, Angelaki, DeAngelis 2008). Similarly, neurons in middle temporal (MT) cortex are tuned to depth based on binocular disparity or motion parallax, and the preferred depths from different modalites can also be congruent or opposite (Nadler et al 2013). These are examples of neuron in the brain that respond to inputs from multiple sensory modalities, e.g., vision, audition, and touch, or from multiple unisensory cues. While the congruently tuned neurons appear natural for the functional role of cue integration, the oppositely tuned neurons appear somewhat puzzling. I propose that, together, congruent and opposite cells in a neural population achieve efficient coding given incomplete redundancy in the input sources (Barlow, 1961). Efficiency requires creating representations (also called bases) in which the inputs are decorrelated. For two sources, this implies two bases in which inputs that sample the features from the two sources are either (weighted and) added or (weighted and) subtracted; these are the genesis respectively of congruently and oppositely tuned cells. The opposite cells are needed because the two sources are typically only incompletely redundant, and their activities can encode input information not encoded by the congruent cells. The exact forms (i.e., relative weighting of the sources) of, and neural sensitivities to, individual bases should depend on, and adapt to, the statistical properties of the inputs (e.g., the correlation between the sources and the signal to noise ratios). Coding of visual-vestibular heading direction and stereoscopic-motion-parallax depth both become analogous to efficient stereo coding in the primary visual cortex (Li & Atick 1994), which represents inputs to the two eyes by the sum and difference of these inputs (which are then multiplexed in the responses of the neural population). Generalization to more than two senses or modalities is straightforward. For example, coding of inputs from three sources can be analogous to efficient color coding of inputs from three cone types (Atick, Li, Redlich 1992), so that there will be three decorrelated channels: a weighted sum and two weighted differences of the three input sources. I will illustrate with some examples and relate them with experimental data.

Disclosures: L. Zhaoping: None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.03/GG23

Topic: D.10. Multisensory Integration

Support: Key Research Program of Frontier Sciences of the Chinese Academy of Sciences QYZDY-SSW-SMC001

National Basic Research Program ("973" Program) of China 2013CB329501

Title: Visual-proprioceptive integration and hand ownership in monkeys and humans

Authors: W. FANG[1,2], J. LI[3], *L. WANG[3]
[1]Inst. of Neuroscience, Key Lab. of Primate Neurobiology, CAS Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., shanghai, China; [2]Key laboratory of Brain Functional Genomics, Inst. of Cognitive Neuroscience, Sch. of Psychology and Cognitive Science, East China Normal Univ., Shanghai, China; [3]Inst. of Neuroscience, Chinese Acad. of Scie, Shanghai, China

Abstract: The ownership of body parts is a fundamental aspect of way we consciously experience our bodies, that is assumed to rely on the integration of sensory signals from multiple modalities. Although the sensory of ownership has been shown in both human and non-human primates, we still know little about how multisensory integration contributes to the feeling and controlling of own bodies. When moving hands to reach a target, subjects combine visual and proprioceptive signals to estimate arm's position. Here we used a virtual reality system and a reaching task to examine the proprioceptive drift, an objective and quantifiable behavioral correlate of the body ownership, in both monkeys and humans. We demonstrated that in both species, the self-location of an upper limb was spatially drifted when the spatial information of visual and proprioceptive signals was relatively matched, and such drift was disrupted when the multisensory conflicts significantly increased. The behavioral pattern of proprioceptive drift was well depicted by Bayesian Causal Inference model. Thus, the results suggest that the relative weighting of vision and proprioception during the integration may lead to the changes of body ownership in both monkeys and humans, which paves our way for further exploring neural mechanisms of bodily self-consciousness at the neural level in animals.

Disclosures: W. Fang: None. **J. Li:** None. **L. Wang:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.04/GG24

Topic: D.10. Multisensory Integration

Title: Does sound pitch and location influence visual motion direction judgments?

Authors: *.. PRACHI[1], S. L. PRIME[2]
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Abstract: Prior research has shown that auditory pitch can influence spatial and motion estimates of visual stimuli. Crossmodal correspondence between pitch and visual space show high pitch sounds are associated with upper space and low pitch sounds with lower space (Evans & Treisman, 2010). Ambiguous motion stimuli are perceived as moving upward when paired with ascending pitch sounds and downward with descending pitch sounds (Carnevale & Harris,

2016; Maeda, Kanai, & Shimojo, 2004). However, the extent to which pitch sounds influence unambiguous visual motion remains unclear. Also, how manipulating both a sound's pitch and spatial location (i.e., the pitch-space relationship) might influence visual motion perception has not been explored before. In this study we investigated how changes in pitch tones affect visual motion direction judgments while varying visual motion saliency and the pitch-spatial location relationship relative to the direction of a visual motion stimulus. Here, subjects were presented with high (1300Hz) or low (300Hz) pitch tones with a random dot kinematogram (RDK) stimulus displaying upward or downward motion. The saliency of visual motion was manipulated by systematically varying the level of coherent motion between 0, 4, 6, 8, and 10% coherence. In Experiment 1, the auditory stimuli were presented from both speakers placed horizontally, left and right of the RDK stimulus. In Experiment 2, the auditory stimuli were presented from either a speaker above or below the RDK stimulus. Subjects had to judge the direction of the coherent motion dots by a 2AFC response (up or down). Experiment 1 showed subjects were more likely to judge the direction of visual motion as going up with high pitch tones and down with low pitch tones. Our results also show this effect for pitch on direction judgments increased as coherence decreased. In Experiment 2, we found an interaction of sound location and pitch (e.g., low pitch tones from the bottom speaker yielded greater judgment bias than low pitch tones from the top speaker). These findings suggest that the extent pitch affects visual motion perception depends on the saliency of the visual motion signal and this pitch effect is sensitive to the pitch-space correspondence.

Disclosures: .. Prachi: None. **S.L. Prime:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.05/GG25

Topic: D.10. Multisensory Integration

Support: NIH Grant DC013906

Title: A dynamic neural code may underlie multisensory integration and segregation in the primate superior colliculus

Authors: *J. T. MOHL, S. TOKDAR, J. M. GROH
Duke Univ., Durham, NC

Abstract: At the neural level, multisensory integration has typically been characterized in relation to either enhancement over the strongest component unisensory response (including linear summation of component responses), or as a weighted averaging computation between the unisensory responses (alternatively referred to as suppression, as it suppresses activity below the

best unisensory response). This averaging effect is particularly common in conditions of cue conflict, such as mismatched visual and vestibular cues or misaligned lights and sounds. However, these perspectives are incompatible with situations where multiple stimuli are represented simultaneously but separately, a prerequisite for perceiving multiple discrete sensory objects. One alternative possibility is that only one stimulus is encoded by each neuron or population at a given time, and that switching between these representations results in apparent averaging when activity is pooled across time or multiple experimental trials.
To probe this question, we required monkeys to localize either visual only, auditory only, or simultaneously presented visual and auditory stimuli at varying locations in space, while we recorded the activity of superior colliculus neurons. We analyzed this neural data using a novel statistical method capable of characterizing neural responses at the single trial level (Caruso et al., biorxiv 2017). We found that responses on combined modality trials often showed activity fluctuations across trials consistent with time-division multiplexing of the individual modalities, rather than averaging or summation of auditory and visual responses. This suggests the existence of a dynamic neural code that retains information about both components of multimodal stimuli.

Disclosures: **J.T. Mohl:** None. **S. Tokdar:** None. **J.M. Groh:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.06/GG26

Topic: D.10. Multisensory Integration

Support: NIH EY022979

Simons Collaboration on the Global Brain

Title: Multisensory enhancement during audiovisual looming responses in mice

Authors: *A. L. JUAVINETT[1], G. BEKHEET[1,2], A. K. CHURCHLAND[1]
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Northeastern Univ., Boston, MA

Abstract: Multisensory integration is a fundamental computation that animals use to navigate their environment, avoid predators, and find prey. Despite a large body of work on multisensory behavior in humans, we do not have a clear map of the circuits and cell types that enable animals to effectively combine stimuli across sensory modalities. While the mouse model allows for targeted circuit interrogation, studying multisensory integration in mice using traditional psychophysical paradigms has proved difficult. We therefore characterized an innate behavior that will serve as a rich platform to investigate multisensory processing in rodents.
When approached overhead, prey either freeze to avoid being seen or escape to a safe place.

Remarkably, even simplified expanding discs commonly called “looming stimuli” reliably elicit freezing and escape responses in mice without prior stimulus exposure . Still, it is unknown whether mice demonstrate multisensory enhancement with the addition of a looming sound to the visual stimulus or which circuits underlie the integration of visual and auditory information--especially since a retinofugal pathway has been proposed as playing a major role in the behavior. To this end, we modified traditional visual looming stimuli to generate a novel multisensory paradigm. While the mouse was freely exploring an arena we presented visual or audiovisual stimuli: looming dots of varying contrasts sometimes paired with increasingly loud white noise. We optimized the speed of our stimulus to elicit robust escape responses to a nest. We measured the animal’s escape velocity, latency to return to the nest, and probability of returning to the nest, allowing us to make several observations: 1) High contrast stimuli elicit faster and more frequent escapes than low contrast stimuli. 2) Mice respond more strongly to looming than receding stimuli, which serve as a control. 3) Mice show a consistent multisensory enhancement, with faster and more frequent escapes in response to audiovisual stimuli.
Our work describes an innate behavior that will enable a mechanistic investigation of multisensory integration in an ecologically-valid context. Future experiments will investigate the neural underpinnings of this behavior using inactivation as well as electrophysiological recordings.
Keywords: multisensory integration, mouse vision, innate behavior, auditory, visual, audiovisual

Disclosures: **A.L. Juavinett:** None. **G. Bekheet:** None. **A.K. Churchland:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.07/GG27

Topic: D.10. Multisensory Integration

Title: Encoding of trial initiation in retrosplenial cortex during navigation in virtual reality

Authors: *L. FISCHER, M. T. HARNETT
MIT, Cambridge, MA

Abstract: Navigation through space requires the combination of knowledge about the surrounding environment with sensory and self-motion information to plan and execute specific trajectories. The retrosplenial cortex (RSC) is hypothesized to play an important role in this process by translating between allocentric and egocentric frames of reference during navigation. To do so, different streams of input, such as visual cues or motor information related to locomotion, need to be integrated. However, the mechanisms mediating this functionality have remained elusive. We have developed a spatial task in virtual reality that requires head-fixed mice to integrate visual, spatial, and self-motion information to locate a rewarded zone along a

linear corridor. Simultaneous 2-photon Ca^{2+} imaging of neurons in area A30 of the RSC allowed us to identify functional cell populations correlated with behavior. One striking response pattern were cells that robustly encoded the onset of a trial. These neurons were active whenever an animal initiated a new trial. However, depending on whether the rewarded zone was marked with a visual cue, or animals had to use self-motion information to locate the reward location, different ensemble dynamics emerged. A separate population of cells estimated the location of transition points between trials when no visual indication was available, but locked their activity to the transition point if there was. Interestingly, axonal boutons projecting into A30 from primary visual cortex showed similar sensitivity to transition points of trials. Two further A30 neuronal subpopulations were identified: cells robustly encoding or predicting rewards, and cells selectively active during traversal of the virtual corridor. Together these results describe the cell type(s) and spatial relationships between neurons in A30 of RSC for encoding multiple task-relevant variables. Encoding of trial onsets suggests a role in planning an upcoming trajectory through space, requiring the integration of spatial knowledge about the environment to translate it into a motor plan via an egocentric frame of reference.

Disclosures: L. Fischer: None. **M.T. Harnett:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.08/GG28

Topic: D.10. Multisensory Integration

Support: Wellcome Trust 095668

Wellcome Trust 095668

Marie Curie Actions 705391

Sir Henry Wellcome Fellowship 110120

Title: Multisensory spatial integration in a two-alternative forced choice task for head-fixed mice

Authors: *P. COEN, M. J. WELLS, M. CARANDINI, K. D. HARRIS
Univ. Col. London, London, United Kingdom

Abstract: The ability to combine information across different sensory modalities and better localize an object in space provides a critical survival advantage to many organisms, whether prey, predator, or pedestrian crossing the street. Most commonly, this process involves the combination of visual and auditory information into a single estimate of an object's location. The neural mechanisms underlying this form of audiovisual integration have been studied in several

species, primarily using detection and orienting tasks in freely moving animals. Such tasks have identified roles for cortical regions and subcortical structures. However, these effects have yet to be evaluated with modern recording techniques that allow comprehensive and reversible inactivation across cortex, as well as the opportunity to record from large neural populations. To probe the role of cortex in audiovisual spatial integration with two-photon calcium imaging and scanning optogenetic inhibition techniques, we have developed a two-alternative forced choice behavior for head-fixed mice. Our multisensory task builds on a previously established visual task (Burgess et al., bioRxiv, 2016), wherein the mouse must move a Gabor patch towards the center of its visual field by turning a wheel placed under its forepaws. We modified this task by adding an array of speakers, arranged radially with respect to the mouse's head, and presenting audiovisual stimuli—consisting of filtered pink noise and a visual Gabor, flashing synchronously at a rate of 5 Hz. Again, the mouse's goal was to move this stimulus to the center of its visual field, and both auditory and visual stimuli moved as the mouse turned the wheel. 5 of 6 mice learned this task within 5 days of training, and generalized to both individual sensory modalities without further training. When presented with a combination of unisensory and multisensory trials, mice perform above chance levels in all conditions, and exhibit enhanced performance and faster reaction times on coherent multisensory trials. We are currently exploring which strategy mice use to integrate information across these sensory modalities. Prior work in our lab has demonstrated that visual cortex is required for the visual version of this task (Zatka-Haas et al, SfN 2016). Thus, we anticipate that cortical regions will be critical for the multisensory enhancement we have observed. With this novel task design, we can now use scanning optogenetic inhibition to identify these regions, and calcium imaging to examine the corresponding neural activity.

Disclosures: P. Coen: None. **M.J. Wells:** None. **M. Carandini:** None. **K.D. Harris:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

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Program#/Poster#: 686.09/GG29

Topic: D.10. Multisensory Integration

Support: NSFC31301882

China Postdoctoral Science Foundation 2013M542301

Title: The action potential diversity of pit-viper's infrared neurons to different wavelength stimuli

Authors: *Q. CHEN, Y. LIU, L. DING, Y. TANG
Chengdu Inst. of Biology, Chinese Acad. of Sci., Sichuan, China

Abstract: The infrared sensor system of the pit-viper is a radiation receptor on broad spectrum. In the testing of neural activities on short-tailed pit-viper's tectum, we found that not only the warm object (such as human's hand, or hot water) could evoke the action potential of the infrared neurons, and the LED flashlight could affect the neural activity also. On the contrary, a LED light-compensating lamp for night-time shooting but cannot evoke the neural activity of infrared neuron. For this reason, the intensity of radiation was supposed to the key to the infrared neurons. Here we use three LED laser on different wavelength (405nm, 650nm, 830nm) as the stimuli for testing the neural activities of snake's tectum. The lenses in front of lasers could adjust the intensity for registering the aim temperature, and a shutter between the laser and snake could control the flash duration of stimuli. In this way, the neural activities would be tested in different wavelength and different temperature. The results showed that, the different color lasers evoked different performance of spike even in the same temperature level. And the patterns of neural activities might be changed among different heat effects. As a consequence, the function of the pit sensor may be the compound action of thermal and photochemical mechanisms.

Disclosures: Q. Chen: None. **Y. Liu:** None. **L. Ding:** None. **Y. Tang:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.10/GG30

Topic: D.10. Multisensory Integration

Support: NIH intramural award to MS

Title: Multimodal sensory responses in neurons of the subesophageal ganglion

Authors: K. SUN, *M. A. STOPFER
NICHD, NIH, Bethesda, MD

Abstract: To generate useful neural representations of the world animals often need to integrate multiple forms of sensory input. To better understand the integration process we identified and characterized multimodal neurons in the brains of the moth *Manduca sexta*. The insect subesophageal ganglion (SEG) receives direct projections from the mouthparts, and is often regarded primarily as a gustatory center. Notably, we found that most neurons we tested throughout this brain area respond vigorously to other sensory modalities, primarily vision. We developed a new apparatus to deliver controlled patterns of taste, light, and odor stimuli to awake moths while making intracellular recordings with sharp electrodes from the SEG. In sequential recordings electrodes were placed blindly throughout the ganglion, usually into neural processes. We recorded from 175 neurons, filled 32 with dye for subsequent reconstruction, and, in five cases, immunostained to test for the inhibitory neurotransmitter GABA. All but two of the

filled neurons showed extensive branching within the SEG; most had somata near the mushroom body or antennal lobe.
Notably, about 86% of the 175 cells we tested showed clear excitatory or inhibitory responses to a 1s flash of light. SEG neurons in moths (N=4) from which either the left or right optic laminae had been removed responded to light, but SEG neurons in moths (N=5) with bilateral lesions did not. Thirteen filled cells extended processes directly to the eyes.
About 60% of tested neurons responded with excitation or inhibition to 1s puffs of odor (hexanol), but only about 38% of tested neurons responded to 1s pulses of tastant (1M sucrose or 1M NaCl). About 32% of tested neurons responded to separate presentations of light and tastant, and about 24% of tested neurons responded to separate presentations of odor and tastant. About 22% of tested neurons responded to all presented visual, taste, and odor stimuli. (We are presently testing additional stimuli alone and in combinations.) Of five multimodal neurons immunostained, none was positive for GABA.
Consistent with recent results from Drosophila larvae (Tastekin et al, 2015), our results suggest the subesophageal ganglion is a multimodal structure that integrates primary sensory inputs.

Disclosures: K. Sun: None. **M.A. Stopfer:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.11/GG31

Topic: D.10. Multisensory Integration

Support: NICHD Intramural Grant to MS

Title: Spatiotemporal coding of taste stimuli

Authors: *A. BORONAT-GARCÍA[1], S. REITER[2], K. SUN[1], M. A. STOPFER[1]
[1]NICHD/NIH, Bethesda, MD; [2]Max Planck Inst. for Brain Res., Frankfurt am Main, Germany

Abstract: To study how taste information is encoded by gustatory neurons, our laboratory has developed a set of techniques to deliver different tastants with precise temporal control while making *in vivo* electrophysiological recordings from multiple gustatory neurons before, during and after a stimulus is delivered. Using a relatively simple model organism, the moth *Manduca sexta*, we previously found that populations of gustatory receptor neurons (GRNs) use a spatiotemporal code to form unique representations of individual chemicals rather than taste categories such as sweet, sour, salty, bitter (Reiter et al, 2015). Information from the periphery travels to the sub-esophageal zone (SEZ), where GRNs synapse upon second order neurons (SONs). A given SON responds to more tastants than its pre-synaptic GRNs because SONs integrate, either directly or indirectly, input from multiple types of GRNs. Anatomical

reconstructions and immunostaining of SONs revealed different types of neurons in the SEZ: excitatory and inhibitory local neurons whose projections are restricted to the SEZ, and neurons that send projections either to the brain (ascending projection neurons, PNs) or to the body ganglia (descending PNs). In addition, local field potential recordings from the SEZ revealed tastant-elicited, picrotoxin-sensitive oscillatory synchronization of populations of neurons in the SEZ. However, much remains unknown about the connectivity in the SEZ between local neurons and PNs, how higher brain areas use the information from populations of ascending PN to represent tastant information, and what aspects of the information represented in PN neural activity are necessary for discriminating among tastants. Thus, to understand how gustatory information is transformed as it makes its way though higher brain areas, we are currently studying SEZ circuitry, and identifying and characterizing follower neurons by combining electrophysiological, anatomical and behavioral techniques.

Disclosures: **A. Boronat-García:** None. **S. Reiter:** None. **K. Sun:** None. **M.A. Stopfer:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.12/GG32

Topic: D.10. Multisensory Integration

Support: American Epilepsy Society

Whitehall foundation

Leon Levy Foundation

Title: *In vivo* calcium imaging of CA3: Spatial pattern completion

Authors: *M. A. DUFOUR, R. TUIP, S. SUNDAR, R. ZEMLA, J. BASU
Neurosci., NYU, New York, NY

Abstract: The hippocampal CA3 sub-region, as an autoassociative network, has been proposed to support pattern completion. In particular, spatial representations in CA3 can present stability or undergo transformation in response to increase level of contextual manipulation.We have developed an in vivo head-fixed imaging paradigm to examine pattern separation and completion based population dynamics at cellular and sub-cellular resolution in CA3. In this task mice are exposed to a wide range of contexts where the differences in the multisensory stimuli between each context is gradually varied to different degrees. Under these conditions we are assessing dynamics between stability and remapping based plasticity of spatially tuned sequences of CA3 pyramidal neurons. In addition, we aim to anatomically and functionally map the long-range excitatory and inhibitory entorhinal cortex inputs.

Disclosures: **M.A. Dufour:** None. **R. Tuip:** None. **S. Sundar:** None. **R. Zemla:** None. **J. Basu:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.13/GG33

Topic: D.10. Multisensory Integration

Title: A new model of the superior colliculus and oculomotor cerebellum's interactions and functions provides one unified localization mechanism for visual, tactile, and auditory stimuli: Fitting together the forgotten pieces

Authors: *M. RIGGLE
Causal Aspects, Charlottesvle, VA

Abstract:

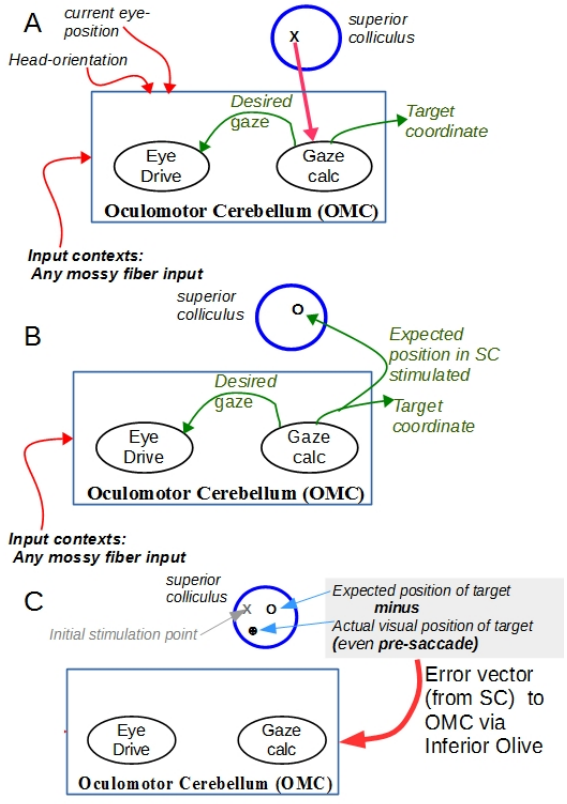

Fig: SC-OMC steps to learn localization.

Very early in fish, the accurate, adaptable visual saccade system evolved -- a system which pairs the superior colliculus(SC) with the oculomotor cerebellum(OMC). In this system, the SC only initiates a saccade, but, after that initiation, the OMC controls the saccade to the end-point. It is the OMC which makes the saccade both accurate and adaptable. Post-saccade, a saccade error is detected by the SC and passed to the OMC which then adjusts to correct the errors. In adaptation, the OMC can use different context inputs (such as eye-position, target velocity, or if you are wearing glasses) on mossy fibers to calculate different end-points for a saccade. This much is established; however, the role of the OMC is much larger. We show (with current supporting evidence) that when a visual target is attended to by the SC, the OMC must produce that target's world coordinate (and the coordinate becomes accurate via the error feedback). Producing correct error feedback from the SC requires the OMC to also calculate the expected position of the target in the SC and to stimulate that position; the SC then uses the difference between the expected position and the actual target to generate an error vector. [Some overlooked relevant OMC elements are: 1) The Head-Orientation-In-World vector is calculated in the OMC and allows the OMC to transform head-relative to/from world frames; 2) The cerebellum's architecture supports recurrent neural-networks].
This SC-OMC capability of using mossy fiber inputs to calculate (and learn) the actual location of visual targets is a reusable mechanism for both auditory and tactile stimuli. The steps to learn any localization (figure 1): A- using inputs, the OMC calculates the target’s world coordinate; B- OMC places expected target into SC; C- SC determines error vector and passes to OMC; last- OMC updates calculation. The steps are the same for visual localization, and tactile and auditory localization if the needed localization data is on mossy fibers - which we show they are.

Disclosures: M. Riggle: None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.14/DP06/HH1 (Dynamic Poster)

Topic: D.10. Multisensory Integration

Support: HHMI

Title: A fundamental circuit mechanism underlying sequences of behavioral actions in *Drosophila* courtship

Authors: *C. E. MCKELLAR[1], J. L. LILLVIS[1], D. E. BATH[1,2], J. G. CANNON[1,3], J. H. SIMPSON[1,4], B. J. DICKSON[1]
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Abstract: Goal-directed animal behaviors are typically composed of sequences of motor actions, the precise order and timing of which can be critical for a successful outcome. Although much current work investigates neural mechanisms underlying complex behaviors, it is largely unknown how the brain assembles discrete actions into sequences for goal-directed behaviors. Here, we identify a recurring behavioral motif of three coordinated actions that male *Drosophila melanogaster* flies perform as they engage with a female during the late stages of courtship. The features of this motif suggest that it may be generated by a ramp-to-threshold mechanism, in which the increasing activity of a central coordinator elicits each action at successively higher activity thresholds. We describe a pair of descending neurons in the fly brain, aSP22, that act as such a central coordinator. Genetic ablation of aSP22 impairs all three actions of the engagement motif, whereas optogenetic activation of aSP22 elicits each action. Each action is triggered at a different activation threshold, with thresholds increasing in the order in which these actions occur within the engagement motif of natural courtship behavior. In biology, morphological patterns are often created through differing response thresholds to a single organizing activity that is spatially or temporally graded. Our findings reveal how an analogous mechanism is employed to assemble discrete motor actions into a recurring motif within a complex behavioral pattern.

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Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.15/HH2

Topic: D.10. Multisensory Integration

Support: NIH Grant F31NS093873

NIH Grant R01NS086859

Title: Early integration of temperature and humidity stimuli in the *Drosophila* brain

Authors: *D. D. FRANK, III[1], A. ENJIN[2], G. C. JOUANDET[1], E. E. ZAHARIEVA[1], A. PARA[1], M. C. STENSMYR[2], M. GALLIO[1]
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Abstract: Many terrestrial organisms can only prosper within a specific range of air humidity. For example, small poikilotherms like *Drosophila melanogaster* risk desiccation (and death) when exposed to hot, dry conditions even for relatively short periods of time. Hence, a fly's

ability to detect and appropriately respond to humidity changes can be critical for survival. The Drosophila antenna is a hub for the senses, containing receptor neurons for mechanical, olfactory, thermal and humidity stimuli. Neurons expressing the ionotropic receptor IR40a have been recently implicated in the selection of an appropriate humidity range, but while previous work indicates that insect hygroreceptors may be made up by a 'triad' of neurons (with a dry- a cold- and a humid-air responding cell), IR40a expression included only cold- and dry-air cells. Here, we report the identification of the humid-responding neurons that complete the hygrosensory triad in the *Drosophila* antenna. Next, we follow the projections of hygrosensory neurons to the brain, and show that they form distinct glomeruli in the posterior antennal lobe. Here, a spatial map of neural activity represents related features of the external environment, with adjacent 'hot', 'cold', 'dry', and 'humid' glomeruli. This organization may allow for both unique and combinatorial sampling by central relay neurons, and we indeed find evidence for each. Our results further our understanding of humidity sensing in the *Drosophila* antenna, uncover neuronal substrates for the processing of temperature and humidity stimuli in the brain, and illustrate the logic of how ethologically relevant combinations of sensory cues can be processed together to produce adaptive behavioral responses.

Disclosures: D.D. Frank: None. **A. Enjin:** None. **G.C. Jouandet:** None. **E.E. Zaharieva:** None. **A. Para:** None. **M.C. Stensmyr:** None. **M. Gallio:** None.

Poster

686. Cross-Modal Processing: Spatial Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 686.16/HH3

Topic: D.10. Multisensory Integration

Support: Margarete von Wrangell Program

Title: Projections of the diencephalospinal dopaminergic system to peripheral sense organs in larval zebrafish (Danio rerio)

Authors: *M. HAEHNEL[1], W. DRIEVER[1,2]
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Abstract: Diencephalic descending dopaminergic neurons in the zebrafish, which are located in the posterior tuberculum and hypothalamus, depend on the transcription factor Orthopedia and are homologues to the mammalian A11 dopaminergic group. Catecholaminergic projections in the central nervous system of larval zebrafish are characterized, and the A11 homologue groups were shown to send projections to the subpallium, endohypothalamic tract, rhombencephalon, and spinal cord. Although, there is evidence that the descending dopaminergic system of larval

zebrafish sends projections to peripheral sense organs, and particularly neurons with large cell bodies in the anterior part of the posterior tuberculum contact neuromasts of the posterior lateral line, a detailed anatomical analysis of dopaminergic projections to targets in the peripheral nervous system is yet missing.
We therefore investigated in detail peripheral catecholaminergic projections in larval zebrafish, adapting the recently developed tissue clearing method CLARITY for use in 3-8 days old zebrafish larval whole mounts to resolve the peripheral projections of the dopaminergic A11 system. To label dopaminergic projections, we used *Tg(th:Gal4-VP16)*^{m1233Tg} and *Tg(UAS:eGFP-CAAX)*^{m1230Tg} transgenic zebrafish to express membrane tagged GFP in dopaminergic neurons. We also combined the *th:Gal4* driver with *Tg(UAS:SypGFP, clmc2:EGFP)*^{m1238Tg} to label presynaptic dopaminergic structures. We focused on the lateral line but also consider connections to the auditory, vestibular and trigeminal system. Our data reveal extensive peripheral diencephalic DA projections to all lateral line organs. In the posterior lateral line, dopaminergic axons project along the posterior lateral line nerve. Single dopaminergic neurons project to multiple lateral line organs, but individual organs may also receive input from distinct dopaminergic neurons. Synaptophysin:GFP label suggests that dopaminergic neurons establish synapses with hair cells. Mapping of dopaminergic axons and synapses reveals that modulation of sensory information may not only occur at the sense organ, but also at the levels of lateral line ganglia and their projection fields in the rhombencephalon. Dopaminergic neurons therefore are likely to play an important role in efferent modulation of sensory systems. Together with recent work revealing lateral line sensory related activity of specific A11 type posterior tubercular dopaminergic groups in zebrafish (Reinig *et al.*, Current Biology 2017); our findings suggest that these dopaminergic neurons are potentially involved in some type of feedback regulation of the lateral line system.

Disclosures: M. Haehnel: None. **W. Driever:** None.

Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 687.01/HH4

Topic: D.10. Multisensory Integration

Support: Northeastern University - Advanced Research / Creative Endeavors Award

Title: Frequency characteristics of thalamocortical pathways involved in affective pain: The mediodorsal/anterior cingulate cortex axis

Authors: A. F. PAQUETTE[1], *R. W. SIKES[2]
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Abstract: This study focuses on thalamocortical transmission between the mediodorsal and parafascicular nuclei (MD/PF) and the anterior cingulate cortex (ACC). Strong reciprocal synaptic connections between these structures exist. Neurophysiological and behavioral studies have established this circuit as crucial in affective pain perception, learning, memory, reward, goal directed activity and attention. Additional studies explored the effect of frequency modulation in the theta range (4-8 Hz) on transmission in this circuit. Modulation of MD/PF activity into theta frequency range potentiates synaptic activation of ACC neurons, and these theta oscillations may allow engagement of functional subregions of ACC. Inflammatory pain can induce a decrease in functional connectivity in this circuit that is strongest in the theta range. The current study explores changes in simultaneously recorded activity of neurons in MD/PF and ACC measured before and during wide spectrum auditory stimulation.
Using 4 anesthetized Long-Evans male rats in the initial study (1.5% halothane), guide cannulas were surgically implanted over ACC and MD/PF. With stereotaxic control, extracellular recording electrodes (AM systems; 1-5 Mohms) were lowered into ACC and MD/PF. Spontaneous activity and a series of auditory evoked activity trials were recorded in both target structures simultaneously. Specifically, field potentials and multicellular action potentials were recorded using the Plexon Map data acquisition system. The action potentials were further resolved into single neuron activity using cluster cutting (Plexon Offline Sorter). Power spectrum and peristimulus histogram analysis were used to analyze the neural activity (Neuroexplorer software).
In initial data from 22 neurons (10 in ACC and 12 in MD/PF), significant responses to auditory stimulation were observed in 4 MD/PF neurons and 0 ACC neurons. Power spectral analysis of spontaneous field potentials in ACC and MD/PF showed more power in delta frequency range (0-4 Hz). During auditory testing the power spectra of ACC field potentials remained in delta range, but shifted to higher delta and theta frequencies in MD/PF. Thus, absence of ACC response may reflect a failure of thalamocortical transmission between these anatomically connected structures due to mismatch of their resonant frequencies. If true, this explanation concurs with previous findings, suggesting functional connectivity among MD/PF and ACC requires resonant frequencies between both structures to be in the theta range.
All experimental procedures were approved by Northeastern University Institutional Animal Care and Use Committee.

Disclosures: **A.F. Paquette:** None. **R.W. Sikes:** None.

Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 687.02/HH5

Topic: D.10. Multisensory Integration

Title: Simultaneous intrinsic imaging of auditory and visual cortex releals cross-modal interactions

Authors: *M. TEICHERT[1], J. BOLZ[2]
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Abstract: In their natural environment animals and humans simultaneously receive multimodal sensory inputs. The primary sensory cortices where these inputs are initially processed are anatomically separated. However, previous studies found intracortical connections between these early sensory cortices suggesting a multimodal interplay (Falchier et al., 2002; Cappe and Barone, 2005; Campi et al., 2010). For example, electrophysiological results obtained in rodents indicate that auditory stimulation can modulate visually evoked V1 responses and affect visual processing (Iurilli et al., 2012; Ibrahim et al., 2016). However, the consequences of an acute loss of one sensory modality on multisensory processing and, particularly on stimulus evoked processing in the spared senses, remain elusive. Here we investigated the early effects of acute hearing loss on visual processing in adult mice. To address this question at the functional and systemic level, we used intrinsic optical imaging which provides high resolution recording over a large field view. Thus, it reflects a population response of many neurons to external stimuli (Kalatsky and Stryker, 2003). First, we developed a method to simultaneously map the primary auditory (A1) and visual cortex (V1) using periodic intrinsic optical imaging. We found that reducing sound evoked A1 responsiveness due to the induction of conductive hearing loss (CHL) led to a concomitant increase of visually driven V1 activity. Accordingly, using the neuronal activity marker c-fos we found the number of stained pyramidal cells to be increased in V1 layer 2/3 after CHL. In contrast, numbers of c-fos positive parvalbumin (PV) and somatostatin (SOM) expressing inhibitory neurons were reduced after CHL. Finally, we adapted the periodic intrinsic imaging method to determine V1 contrast and spatial frequency tuning. Using this method we could show that cortical spatial resolution and contrast sensitivity were improved after immediately CHL. In addition, retrograde tracing experiments revealed direct anatomical projections from A1 to V1 which could potentially serve as a substrate for the observed effects. Taken together, our data suggest that an interplay of an intact auditory and visual sense controls evoked activity in V1. However, if the auditory input is deprived the brake of visually driven V1 activation is rapidly released suggesting a disinhibitory effect which leads to increased evoked V1 responses. We conclude that CHL rapidly disrupts the functional interplay between A1 and V1 leading to altered visually evoked V1 responses.

Disclosures: **M. Teichert:** None. **J. Bolz:** None.

Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

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Program#/Poster#: 687.03/HH6

Topic: D.10. Multisensory Integration

Support: KAKENHI 15H03126

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MHLW/AMED grant (BMI)

MEXT/AMED-SRPBS grant (BMI)

Title: Effect of vision of arm posture on a crossed hands illusion task in an amputee

Authors: *Y. SATO[1], T. KAWASE[1,2], K. TAKANO[1], K. KANSAKU[1,3]
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Abstract: When successive somatosensory stimuli are delivered one to each hand at moderately short intervals (< 300ms) with eyes closed, crossing the arms causes inverting of the temporal order (a crossed hands illusion task; Yamamoto and Kitazawa, 2001a). Similar stimuli were delivered to the tips of two drumsticks, one held in each hand, and the research group reported a similar illusion with the drumsticks crossed (Yamamoto and Kitazawa, 2001b). In our previous experiment, we applied the crossed hands illusion task to an amputee with a functional prosthetic arm, and found that the reversal illusion was significantly larger in an experimental condition with the prosthetic arm than in a control condition without the prosthetic arm (Sato et al., 2016). In this research, we investigated the effect of vision of arm posture on a crossed hands illusion task in an amputee participant. In an experimental condition, a left arm amputee wore a long prosthesis and judged temporal order of two successive tactile stimuli, one delivered to a socket of the prosthesis and the other to the third finger of the right hand. A dummy stimulator was placed at the tip of the prosthesis. When crossing the arms, the participant crossed the long left prosthetic arm on the right arm. In a control condition, the participant wore a short prosthesis and judged temporal order of two successive tactile stimuli, one delivered to the socket of the prosthesis and the other to the third finger of the right hand. A dummy stimulator was placed at the tip of the prosthesis. When crossing the arms, the position of his arms were same, but the short left prosthesis did not reach to the right arm.In both conditions, first, the participant was asked to perform the task with their arm uncrossed and crossed, with eyes closing. Then we asked the participant to open eyes to see the arm position, and again perform the task with

closing eyes. Degree of the reversal illusion was calculated as the differences between correct response rates of the arms crossed and those of the arms straight (Yamamoto and Kitazawa, 2001a). The degree of the reversal illusion with and without vision of the arm posture was evaluated, and the illusion induced by the vision was significantly larger in the experimental condition with the long prosthetic arm than in the control condition with the short prosthetic arm ($p < 0.05$). The results suggest the importance of vision of arm posture to the crossed hands illusion. Note that the tactile stimuli delivered and the arm posture were same in both conditions, but only vision of the prosthetic arm posture was different. The amputee may feel the tactile stimuli at the tip of the prostheses.

Disclosures: Y. Sato: None. **T. Kawase:** None. **K. Takano:** None. **K. Kansaku:** None.

Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

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Topic: D.10. Multisensory Integration

Support: National Institute of Health Center Grant U54 HD083211

CTSA Award KL2TR000446

US DOE Preparation of Leadership Personnel H325D140087

Title: Associations between sensory integration and sensory responsiveness in children with autism spectrum disorder

Authors: *J. I. FELDMAN[1], W. KUANG[1], D. M. SIMON[1], J. G. CONRAD[1], P. SANTAPURAM[1], A. TU[1], M. T. WALLACE[2], T. G. WOYNAROSKI[3]
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Abstract: Children with autism spectrum disorder (ASD) differ in multisensory integration relative to typically developing (TD) peers. For example, in comparison to TD controls, children with ASD may show a reduced magnitude of integration for audiovisual speech, binding of audiovisual speech cues over an atypically wide window of time, and difficulty in perceiving speech in both visual only and matched audiovisual conditions. Children with ASD also show differences in their patterns of responses to sensory stimuli (i.e., sensory responsiveness) relative to TD peers. This study explored the extent to which multisensory speech perception and integration correlated with patterns of sensory responsiveness in children with ASD and TD children. Participants were 18, 8-17 year old children with ASD and 18 TD controls matched on chronological age, sex, and IQ. To assess multisensory speech perception and integration, we

utilized a psychophysical task, wherein participants were randomly presented with CV syllables (e.g., ba, ga) in auditory only, visual only, matched AV, and mismatched AV (visual ga + auditory ba; McGurk) conditions. To evaluate the effects of temporal asynchrony on binding of multisensory speech information, the timing of the mismatched auditory ba and visual ga stimuli was shifted so that the visual stimulus preceded the auditory stimulus by seven stimulus onset asynchronies (SOAs): 0 ms, 33, 66, 100, 166, 233, and 300 ms. Two parent report measures were used to measure sensory responsiveness. Several indices of multisensory speech perception/integration were associated with patterns of sensory responsiveness. Hyporesponsiveness (reduced responding to sensory stimuli) correlated with TBW size (r = .39), as well as accuracy in the auditory only (r = - .35), visual only (r = - .48), and matched AV (r = - .51) conditions. Hyperresponsiveness (exaggerated responding to sensory stimuli) correlated with accuracy in the visual only (r = - .52) and matched AV (r = - .36) conditions. Sensory seeking (fascination with/craving of certain sensory experiences) correlated with TBW size (r = .35) and accuracy in the auditory only (r = - .29), visual only (r = - .29), and matched AV (r = - .43) conditions. Regression analyses indicated that none of the aforementioned associations were moderated by group. is the first study to demonstrate that differences in multisensory speech perception and integration covary with atypical patterns of sensory responsiveness. Additional work is needed to determine whether differences in multisensory speech perception temporally precede, or are causally related to, differences in sensory responsiveness, or vice versa.

Disclosures: **J.I. Feldman:** None. **W. Kuang:** None. **D.M. Simon:** None. **J.G. Conrad:** None. **P. Santapuram:** None. **A. Tu:** None. **M.T. Wallace:** None. **T.G. Woynaroski:** None.

Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

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Program#/Poster#: 687.05/HH8

Topic: D.10. Multisensory Integration

Title: Audiovisual stimulus correlation drives multisensory perceptual decisions

Authors: *A. R. NIDIFFER, R. RAMACHANDRAN, M. T. WALLACE
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Abstract: Sensory signals originating from the same event, such as the voice and mouth movements of a speaker, are often temporally correlated. It is hypothesized that the brain evaluates these correlations to facilitate feature integration and binding within and across sensory modalities. Previous studies have shown that correlation between unisensory signals facilitates several multisensory behaviors, whereas uncorrelated signals do not. In the current study, we sought to further illuminate the nature of this relationship, hypothesizing that multisensory

behavior will vary with the strength of correlation. To this end, we presented participants with sinusoidal amplitude modulated auditory and visual stimuli at modulation depth thresholds. Participants reported the presence or absence of modulation in either stimulus. On a trial, modulation was present in auditory, visual, both, or neither modality (10% of the total trials, catch trials). On audiovisual trials, visual modulation frequency and phase were constant while auditory modulation frequency and phase were varied to generate stimulus pairs with a range of temporal correlations. Accuracy and reaction time data were fit to a drift diffusion model in which non-decision time and drift rate could vary across conditions. The pattern of discriminability and drift rate across conditions was very similar to that of stimulus correlation, but with an apparent phase shift that reflected unique temporal processing of the unisensory stimuli across participants. After accounting for this phase shift, drift rate varied with stimulus correlation in every participant, suggesting that stronger stimulus correlations provide stronger sensory evidence. In two participants, non-decision time decreased with increased stimulus correlation indicating faster encoding of positively correlated stimuli. These results indicate that the degree of stimulus correlation strongly impacts multisensory perception. Further, they suggest that the process of binding could be stochastically dependent on correlation such that signals are more likely to be bound as their correlation approaches 1.

Disclosures: **A.R. Nidiffer:** None. **R. Ramachandran:** None. **M.T. Wallace:** None.

Poster

687. Cross-Modal Processing: Temporal Factors

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Topic: D.10. Multisensory Integration

Support: NIH Grant U54 HD083211

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Title: Rapid recalibration to asynchronous audiovisual speech modulates the rate of evidence accumulation

Authors: *D. M. SIMON[1], A. R. NIDIFFER[2], M. T. WALLACE[2]
[2]Hearing and Speech Sci., [1]Vanderbilt Univ., Nashville, TN

Abstract: Asynchronous arrival of audiovisual information at the peripheral sensory organs is a ubiquitous property of signals in the natural environment due to differences in the propagation

time of light and sound. Rapid adaptation to these asynchronies is crucial for the appropriate integration of audiovisual cues, and consequently for the creation of a coherent perceptual representation of our dynamic world. We investigated the neural basis of rapid recalibration to asynchronous audiovisual speech using psychophysics, drift diffusion modeling, and electroencephalography (EEG). Consistent with previous reports of rapid audiovisual recalibration, we found that participant's perception of audiovisual temporal synchrony depends on the temporal structure of the previous trial. Drift diffusion modelling indicated that this temporal recalibration effect was well accounted for by trial order dependency in the rate of evidence accumulation (i.e. drift rate). Neural responses as measured via evoked potentials were likewise found to vary based on the temporal ordering of the previous trial. Furthermore, these neural signals displayed both response locking and a build to threshold structure that have previously been established as neural correlate of evidence accumulation. Within and across subject correlational analysis indicated that the observed changes in drift rate and the modulation of evoked potential magnitude were related. These findings indicate that trial-by-trial adaptation to asynchronous audiovisual speech occurs via rapid reweighting of sensory evidence.

Disclosures: D.M. Simon: None. **A.R. Nidiffer:** None. **M.T. Wallace:** None.

Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

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Program#/Poster#: 687.07/HH10

Topic: D.10. Multisensory Integration

Support: NHMRC Grant 1063566

Title: Head impulse saccades are affected differently without vision

Authors: *J. M. POGSON[1,3,4], L. MCGARVIE[2,3,4], R. L. TAYLOR[4], A. P. BRADSHAW[4], G. M. HALMAGYI[1,3,4], M. S. WELGAMPOLA[1,3,4]
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Abstract: The head impulse (HIMP) test reflects the relationship between the vestibulo-ocular reflex and the saccadic system. After peripheral vestibular loss, saccades can redirect gaze during HIMP while the head is still moving (covert saccades) or after the head stops (overt saccades)[1]. Generating covert saccades requires either vision or residual vestibular function[2]. When the head is still, the primary (initial) saccade affects the amplitude and latency of secondary (later) saccades, even without vision, indicating a non-visual map [3 4]. We examined if the same relationship exists between covert primary and overt secondary saccades in the HIMP.We tested

6 normal, 5 post-surgical unilateral vestibular deafferentation (UVD) and 5 bilateral vestibular loss (BVL) subjects. All subjects fixed on a target at a 160 cm. Passive horizontal HIMPs were captured first in light, then in complete darkness as subjects fixed on the imagined target. Head and eye movements were recorded by a video head impulse test system. Saccades occurring during and after the HIMP were classified as “covert” and “overt”. First and later saccades were named “primary” and “secondary”.In both UVD and BVL, mean prevalence of covert primary saccades did not differ between light and dark (UVD - light: 85±21%, dark: 90±11%; p=1, BVL - light: 58±42%; dark: 49±37; p=0.17), but BVL was significantly less than UVD in dark (UVD: 90±11%; BVL: 49±37%; p=0.02). In UVD, prevalence of overt secondary saccades was borderline less in light and dark (light: 89±13; dark: 61±31%; p=0.06), but BVL was significant less in dark (light: 76±21%; dark: 12±10%; p=0.02), also when compared to UVD in dark (UVD: 61±31%; BVL: 12±10%; p<0.01). In BVL, covert primary saccade onset latencies were shorter in dark than light (light: 132±35ms; dark: 120±26ms; p<0.001). UVD latencies were shorter in light (UVD: 123±28ms; BVL: 132±35ms; p=0.04). In UVD, overt secondary saccade onset latencies were shorter in light then dark (light: 355±100; dark: 378±104; p=0.02).In UVD and BVL, covert saccade prevalence is not affected by light but overt saccades are. This data demonstrates a non-visually triggered primary covert saccade, and points to a predominantly visual mechanism for triggering overt saccades. UVD and BVL subjects who can generate covert saccades during HIMPs do not rely on vision alone to redirect gaze. Paradoxically, the triggering of primary covert saccades in light in BVL is *delayed* but in UVD are *hastened*, supporting the multisensory nature of covert saccades. 1. Weber KP, et al., Neurology. 2008;70(6):454-463 2. Lehnen N, et al., Neurology. 2013;81(7):688-690 3. Ohl S, et al., J Vis. 2013;13(5) 4. Tian J, et al., Vis Res. 2013;89:54-64

Disclosures: **J.M. Pogson:** None. **L. McGarvie:** A. Employment/Salary (full or part-time):; GN Otometrics. **R.L. Taylor:** None. **A.P. Bradshaw:** None. **G.M. Halmagyi:** A. Employment/Salary (full or part-time):; GN Otometrics. **M.S. Welgampola:** None.

Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 687.08/HH11

Topic: D.10. Multisensory Integration

Title: Distinct reference frames of visual and vestibular heading signals in macaque FEFsem and MSTd

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Abstract: Precise heading estimate requires integration of visual and vestibular information that originates from distinct spatial coordinates (visual: eye-centered; vestibular: head-centered). To explore whether the two heading signals may share a common reference frame along the hierarchy of cortical stages, we explored two multisensory areas: the pursuit area of the frontal eye field (FEFsem) which is closer to the motor side, and the dorsal portion of medial superior temporal area (MSTd) which is closer to the sensory side. In both areas, vestibular signals are head-centered. Compared to MSTd, visual optic flow signals are less eye-centered in FEFsem, yet still largely apart from the head-centered coordinate. Importantly, the visual reference frame is robust that is independent on: (1) smooth pursuit eye movement, (2) motion parallax, and (3) behavioral context for active heading estimation. Our results suggest that visual and vestibular heading signals may be coded in distinct reference frames in the brain.

Disclosures: L. Yang: None. **Y. Gu:** None.

Poster

687. Cross-Modal Processing: Temporal Factors

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Program#/Poster#: 687.09/HH12

Topic: D.10. Multisensory Integration

Support: B.R.A.I.N. - MH111439

I-CORE 51/11

Title: Time precision of cortico-cortical interactions

Authors: *I. TAL[1,2,3], M. ABELES[3], M. LESZCZYNSKI[2], J. L. HERRERO[4], S. R. JONES[5], C. E. SCHROEDER[1,2]
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Abstract: Cognitive neuroscience aims at understanding how dynamic interactions across neurons implement complex information processing in the brain. Yet, most current electrophysiology analysis methods require averaging over trials or long segments of data and are thus bound to miss the fast dynamics of neural activity. Here, we present an alternative way for studying sequences of cortical activations associated with the task. This approach is based on the hypothesis that when a cortical region starts to engage in a new process, there is a transient increase in neuronal activity lasting until the local inhibitory feedback quenches this activity burst. We report that precise spatio-temporal sequences can be detected in the human brain using noninvasive imaging techniques and relate these events to direct measurements of population

activity in non-human primates. Brain activity was recorded using MEG in subjects performing a sensorimotor synchronization task. The on-going magnetic fields were converted to current-dipoles from multiple points over the brain's hull. Brief activity undulations (BAUs) comprised of 20 msec deflections in the signal were automatically detected across all the current dipoles. Interestingly, the stereotypical shape of these events in the time domain closely resembles bursts of beta events described in previous studies. The times of these undulations were treated as point processes. We then searched for repeating spatio-temporal patterns of these BAUs. Many such repeating patterns were found ranging from repeating triplets of events to repeating patterns of 14 events. The null distribution of the number of repeating patterns was constructed by teetering the timing of the BAUs within ±1 samples resulting in a considerable reduction in the number of repeating patterns indicating the importance of the precise timing of these events. Using this technique, we showed that timing accuracy is better than 3 msec. Next, we asked if we could identify brief increases in local populations activity by direct neuronal recordings. We used linear array multielectrodes to record laminar profiles LFP (augmented by current source density or CSD) and multiunit activity (MUA) from both auditory cortical and frontal areas in behaving monkeys. This work is ongoing, but a potential analogue to the findings has already emerged; particularly in frontal and prefrontal areas, brief beta band, (20 Hz) oscillatory responses evident in both CSD and MUA profiles synchronize to the onset of the stimuli. Increased MUA around these events showed that it is reasonable to treat such transients as markers for the time at which a new wave of activity is elicited in the cortical patch.

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Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 687.10/HH13

Topic: D.10. Multisensory Integration

Support: NIH Grant EY023258

NIH Grant P20 GM103650

Title: Aging impairs lag adaptation but not Bayesian temporal recalibration of sensory and motor stimuli

Authors: *A. N. SCURRY, A. NICHOLSON, M. A. WEBSTER, F. JIANG, T. VERCILLO
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Abstract: Time perception is central to human experience and plays a crucial role in shaping behavior. Temporal perception is actively created by our own minds and like many other perceptual processes can be modulated by internal biological factors. For example, as we age time seems to speed up, as reported by the psychologist William James, and age differences in temporal perception can sometimes be attributed to deficits in other cognitive functions such as attention and working memory. As time perception is not a confined and singular mechanism but rather takes many forms and occurs at different levels of processing, it is difficult to isolate which aspects of time perception are impaired or altered by the aging process. Specifically, it is unclear whether aging has a broad influence on cognition, and therefore on time perception in general, or has a selective impact on distinctive and identifiable mechanisms underlying time perception. In the current study, we tested young and elderly adults in four temporal tasks, each measuring a different aspect of temporal sensitivity and adaptability. We designed three asynchrony tasks (unisensory, multisensory and sensorimotor) to measure temporal sensitivity as the ability to discern the temporal order of two stimuli (visual/visual, auditory/visual, visual/motor), and temporal recalibration as the ability to adjust these temporal judgments after adaptation to an asynchrony between the two stimuli. We also ran a duration task (visual), where we measured sensitivity for duration judgments and duration compression after speed adaptation. Temporal sensitivity decreased with age regardless of the task, suggesting a widespread effect of aging on time perception, most likely reflecting a general cognitive impairment. In contrast, the aging effects on temporal adaptability were task-specific. Temporal recalibration decayed with age for multisensory and sensorimotor, but not for unisensory stimuli. Most importantly, the effect of adaptation agreed with the Bayesian integration theory in the judgment of visual stimuli (unisensory temporal order, visual duration), whereas audiovisual and sensorimotor stimuli were recalibrated following a lag adaptation mechanism (Miyazaki, Yamamoto, Uchida & Kitazawa, 2006). Results from our study show that healthy aging selectively impairs the recalibration of temporal order between sensory modalities and between the sensory and the motor systems, and that a general loss in temporal sensitivity in elderly individuals might be related to an overall cognitive decline. Our results also revealed different mechanisms subserving the perception of time.

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Poster

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Support: NIH/NINDS grant R21 NS086356

U. S. Army Research Office grants W911NF-11-1-0105 and W911NF-15-1-0311

Title: Role of causal information in visual-haptic and visual-kinesthetic cue combination

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Abstract: The causal inference framework of multisensory perception (Körding *et al*., 2007) posits that the brain can infer the causal structure of sensory events from sensory information, and utilize this information during the cue combination process. We investigated the influence of the inferred causal structure during two different multisensory two-alternative force choice (2AFC) tasks. During the visual-kinesthetic task, human subjects freely moved a computer mouse (or joystick, depending on the experiment) and reported which of the two cursors simultaneously visible on a high-speed computer monitor was driven by the mouse. Note that the since the mouse was self-driven, the underlying causal information arises solely from reafferent sources in this case. We systematically varied the temporal parameters of the cursors, including their spatial and temporal jitter (*i.e*., variance), and the degree of synchrony between the mouse and either cursor. We found that when the variance of both cursors was relatively low (temporal jitter of < 4 Hz and/or spatial jitter of < 20 min arc on average), subjects performed well above chance levels ($d' > 2$, $p < 0.05$), as expected. However, with increasing cursor variance, subjects were increasingly likely to perceive the cursor with smaller variance as the one driven by the mouse. Indeed, sufficiently large cursor variance values could significantly override synchrony information ($d' < -2$, $p < 0.05$ at temporal jitter of > 8 Hz and/or spatial jitter of > 60 min arc). Similar results were obtained during a similar visual-haptic task in which the visual object was synchronized with the haptic object in real time using an embedded rotation/position sensor (Hegdé, 2016). Together, these results suggest that brain has an internal estimate of the reliability of its own reafferent information, and can override the inferred causal structure when it is inconsistent with other sensory information.

Disclosures: J. Hegde: None.

Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: D.10. Multisensory Integration

Title: Temporal probabilistic inference in three sensory modalities

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Abstract: Estimating the timing of event onset is fundamental for efficient interaction with the environment. Since fast ecologic cues happen on a short, continuous timescale, the brain has to model densely populated event horizons spanning intervals of several seconds. This temporal-probabilistic inference requires estimation of elapsed time as well as event probability over time. In this work, we study how the brain models these stochastic sources of information in three different sensory modalities, namely vision, audition and somatosensation. Recent work has demonstrated, using specific Probability Density Functions (PDF) of visual events, that reaction times (RT) and neuronal activity are correlated with the Hazard Rate function (HR) (Janssen and Shadlen, 2005), suggesting that this is one of the basic variables employed by the brain in order to model temporal probabilities. However it is unclear whether this relationship generalises beyond these specific PDFs and whether the PDFs themselves and/or their corresponding Cumulative Distribution Functions (CDFs) also contribute to this modeling process in the brain. Additionally it is not known if this process is similar across the different sensory modalities. To address the above standing issues, we extended previous work to different probabilistic structures, investigated each of three different sensory modalities and also performed inter-modal experiments in order to investigate the following questions: i) What variables (HR, PDF, CDF) are used by the brain to model temporal probability? ii) What are the differences in this modeling process between the different sensory modalities? We used several versions of a simple 'set' - 'go' trial structure that encoded different PDFs. We first show that the HR by itself does not accurately explain the observed patterns of RT. We then demonstrate that there are significant differences between modalities, indicating peripheral processing, but also a prevalent common pattern across the three modalities, suggesting shared central processing of temporal probability estimation. Ongoing magnetoencephalography recordings aim to identify the neural correlates of these mechanisms manifested in behaviour.

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Poster

687. Cross-Modal Processing: Temporal Factors

Location: Halls A-C

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Program#/Poster#: 687.13/HH16

Topic: B.09. Physiological Properties of Neurons

Support: Bard Summer Research Intitute

Title: Midbrain neurons show temporal retuning of intrinsic properties in response to patterned uni- and multisensory stimulation

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Abstract: To properly encode and process information within a functional network, neurons should have their intrinsic properties "tuned" according to their role in this network. For example, one can expect homeostatic plasticity to drive spiking thresholds up for neurons that receive stronger synaptic inputs. Similarly, it is conceivable that neurons involved in the temporal analysis of sensory stimuli could preferentially respond to either faster or slower patterns of synaptic activation. In this study, we use the dynamic clamp technique to explore changes in the intrinsic temporal tuning of midbrain sensory neurons in Xenopus tadpoles in response to sensory stimulation. We exposed animals to 3 hours of either visual, acoustic, or multisensory patterned stimulation that included light flashes, looming stimuli, and sound clicks. We then excited tectal neurons with simulated synaptic conductances of different temporal profiles in whole-cell patch-clamp mode, and measured their spike output. We asked whether, compared to controls, neurons in the tectum of tadpoles exposed to patterned stimulation retuned their temporal input-output functions, to potentially better adjust to this stimulation. We found that overall, the spiking in neurons from stimulated animals was homeostatically suppressed. When animals were exposed to looming stimuli, this suppression was weaker than for animals exposed to flashes, despite the fact that looming stimuli are known to induce stronger spiking in the tectum. Moreover, the temporal tuning of neurons in post-flash animals was strongly reshaped: while control and post-looming neurons spiked more in response to slower simulated synaptic conductances that mimicked looming stimuli, post-flash neurons preferred faster simulated inputs that mimicked full field flashes. This suggests that neurons became selective for the temporal stimuli to which they were exposed. We also checked whether acoustic stimulation alone, or a multisensory combination of visual and acoustic stimuli would change temporal tuning in tectal neurons. We found that although the tectum is typically thought of as a primarily visual area, repeated acoustic stimuli reduced tectal excitability, without reshaping temporal tuning. In multisensory experiments, unexpectedly, a combination of sound and visual flashes had a weaker effect on homeostatic suppression than visual flashes alone. The temporal tuning for multisensory stimuli also differed from unisensory, and depended on the delay between acoustic and visual stimuli during training. Finally, we report some of the cellular mechanisms behind these homeostatic changes.

Disclosures: S.E. Busch: None. **A.S. Khakhalin:** None.

Poster

688. Cross-Modal Processing: Humans

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Topic: D.10. Multisensory Integration

Support: KAKENHI(16H01866, 16K12969)

Title: Cross-modal effects in speed judgments during virtual motorcycle riding

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Abstract: During motorcycling, the rider's sense of speed is generated by multimodal information. For example, the sense of speed should be estimated based not only on the optical flow but also on the engine-drive sound and vibration. In what manner do such visual and audio-tactile information affect each other to generate the sense of speed? In the present study, we investigated cross-modal effects using a virtual motorcycle system. In previous studies using basic psychophysical tasks, two opposite types of cross-modal effects have been reported, namely the averaging effect (e.g., Ernst & Banks, 2002) and the contrast effect (e.g., Ho et al., 2014). We stated the two effects as alternative hypotheses. In our experiments, participants wore a head-mounted display (HMD) and earphones, and sat astride a motorcycle-type chassis. The HMD presented a moving scene during motorcycling from a first-person viewpoint. The earphones presented the engine-drive sound. An actuator under the seat of the chassis presented the engine-drive vibration. The sound and vibration were generated by using a common waveform signal for each trial. In Experiment 1, we tested the effect of the speed of the engine-drive sound and vibration on the speed judgment of the moving scene. When the speed of the engine-drive sound and vibration was higher relative to that of the moving scene, the participants (N = 16) judged the speed of the moving scene as higher than the actual speed. However, no effect was observed when the speed of the engine-drive sound and vibration was lower relative to that of the moving scene. In Experiment 2, conversely, we tested the effect of the speed of the moving scene on the speed judgment of the engine-drive sound and vibration. When the speed of the moving scene was lower relative to that of the engine-drive sound and vibration, the participants (N = 16) judged the speed of the engine-drive sound and vibration as lower than the actual speed. However, no effect was observed when the speed of the moving scene was higher relative to that of the engine-drive sound and vibration. Thus, the averaging effect was observed between the visual and audio-tactile modalities in speed judgment during virtual motorcycle riding. Moreover, our results suggest that the averaging effect operated only to accelerate the perceived speed when the visual modality influenced the audio-tactile modalities but only to decelerate perceived speed when the audio-tactile modalities influenced the visual modality.

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Poster

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Topic: D.10. Multisensory Integration

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NSF GRFP

Title: Complementary roles of spatial- and timing-based control during rhythmic arm movements

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Abstract: In the study of online movement control, vision is assumed to dominate and timing is often taken for granted, amounting to an assumption that the brain executes "perfect-time" control [Lavalle & Egerstedt 2007, Lamperski & Cowan, 2016]. Paddle juggling (repeatedly bouncing a ball off a paddle) is a task that is considered predominantly spatially controlled [Siegler et al., 2013; Ronsse et al., 2010], despite the importance of arm movement timing [Schaal et al., 1996]. Moreover, stable paddle juggling behavior has characteristics that cannot be explained by vision alone: skillful juggling can be accomplished in the absence of vision [Sternad et al., 2001], and visuospatial accuracy can be enhanced by providing touch cues [Ankarali et al., 2014].

To study how non-spatial cues affect online control, we designed a virtual reality paddle-juggling task where human volunteers bounced a ball on a monitor using vertical movements of a haptic paddle [Ankarali et al., 2014]. The only explicit goal was spatial: to hit the ball to a peak height of 35 cm. Ball position was displayed visually for 221 ms (13 video frames), centered around the apex of the flight. Ball--paddle collisions were signaled using an audio beep and simultaneous force pulse delivered by the haptic paddle. All experiments were run on a custom hard-real-time platform (40-us precision).

Unbeknownst to participants (n=10 for each experiment), we imposed cycle-by-cycle perturbations of displayed ball peaks and collision cue timings, so that peaks were displayed higher or lower, or timing or cues were rendered earlier or later, than the simulated physics would dictate. Sinusoidal perturbations (+/-3 cm spatial and +/-30 ms timing amplitudes) were used to derive the frequency response of participants' visual and timing-based controllers. These frequency-response functions were fit with parametric models that were then used to predict responses to jump perturbations (+/-4 cm spatial and +/-30 ms temporal).

We found that visuospatial control was best fit by a proportional--integral model, consistent with

previous error correction models. We also uncovered a timing-related controller that, unlike the spatial controller, entrained to error rather than correcting it. Timing control exhibited higher bandwidth than spatial control. Further, frequency-domain spatial- and timing- control models accurately predicted responses to jump ("step") perturbations. These results suggest the brain not only controls movements to attain desired spatial goals, but also solves the temporal problem of synchronizing motor timing with event timing feedback.

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Poster

688. Cross-Modal Processing: Humans

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Topic: D.10. Multisensory Integration

Support: NIH Grant EY025978

Title: Representational similarity analysis of sound symbolic auditory-visual crossmodal correspondences

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Abstract: Humans consistently indicate correspondences between the sounds in a word (e.g. 'loh-moh') and the visual physical shape of objects (e.g. blob). This phenomenon is an example of a sound symbolic cross-modal correspondence. Multiple other examples of cross-modal correspondences between auditory and visual features of objects exist (e.g. low pitch and large size vs. high pitch and small size). Others have investigated auditory-visual cross-modal correspondences and shown that modulating the physical dimensions that define them can influence multisensory integration. In previous investigations, our group and others examined sound symbolic cross-modal correspondences at the level of phonetic categories and found that specific phonetic segments of nonwords are more likely to be consistently rated as rounded or pointed. For example, sonorants like /l/ or /m/ tend to be rated as rounded. We have used the data-driven approach of representational similarity analysis (RSA) to extend these findings linking physical stimulus parameters and perceptual ratings for a range of rounded and pointed auditory nonwords and visual shapes. This approach minimizes the potential for categorization bias. RSA on perceptual ratings of auditory nonwords and visual shapes revealed that the perceptual continuum from pointed to rounded is nonlinear and is variable for some nonwords and shapes but not for others. For nonwords and shapes at or near the extremes of the continuum,

perceptual ratings are highly consistent and invariant regardless of the other stimuli of the same modality that are presented for judgment. For nonwords and shapes around the middle of the continuum, perceptual ratings are less consistent and judgments can be shifted depending on the range and number of the other stimuli presented. Our analysis further indicates that this nonlinear scale of rounded to pointed is evident in certain physical features of the auditory (e.g. speech envelope) and visual (e.g. curvature) stimuli. These connections between the perceptual and physical measurements are being used as models to inform functional magnetic resonance imaging experiments and may be reflected in participants' blood oxygenation level dependent response during presentation of these stimuli. This research provides insights into the fundamental nature of crossmodal correspondences and how they evoke specific interpretations of physical meaning in natural language at the physical, perceptual, and neural levels.

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Poster

688. Cross-Modal Processing: Humans

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Topic: D.10. Multisensory Integration

Title: Task selectivity as a comprehensive principle for brain organization

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Abstract: What are the principles subtending the emergence of brain specializations in the human brain? In the last decades, convergent evidence from studies with sensory deprived populations such as blind and deaf adults showed that most of the known specialized regions in higher-order 'visual' and 'auditory' cortices maintained their anatomically consistent category-selective properties in the absence of visual/auditory experience when input was provided by other senses carrying category-specific information. In this talk I will review this evidence by comparing it with the predictions coming from a prominent theory in cognitive neuroscience, "neural recycling", from the Dehaene group, which postulates that the anatomical consistencies of brain specializations observed when learning new tasks stem from shared basic sensory physical similarities with the original task processed in that specific brain region. I will challenge the sensory-anchored assumption of the neural recycling theory and propose an integrated

framework regarding the principles subtending the sensory brain organization, ultimately supporting the notion of the brain as a task-machine rather than as a sensory machine as classically conceived. Next I will address the case of early sensory cortices as a model to unravel whether the whole brain is a task-machine or this notion explains only the organization of higher-order sensory cortices. I will present evidence suggesting that early sensory cortices re-organization following sensory deprivation and especially blindness, seems to suggest a negative answer to this question as the deprived V1 has been repeatedly shown to be activated by memory and language (task-switching plasticity). However, I will also present recent data challenging this negative conclusion and propose novel ways to conceptualize and test task-machine organization in those cortices. Finally, I will discuss the implications of our results for both basic research and for clinical rehabilitation settings.
For more information see www.brainvisionrehab.com and this additional reading:
Amedi, A., Hofstetter, S., Maidenbaum, S., & Heimler, B. (2017). Task Selectivity as a Comprehensive Principle for Brain Organization. Trends in Cognitive Sciences.

Disclosures: **A. Amedi:** None. **S. Hofstetter:** None. **S. Maidenbaum:** None. **B. Heimler:** None.

Poster

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Topic: D.10. Multisensory Integration

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Title: Handedness-related hemispheric dominance and spatial orientation constancy

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Abstract: There is a significant lateralization in hemispheric contribution to perception of spatial orientation. This functional laterality is primarily localized to the vestibular cortical network with a handedness-related functional dominance in the non-dominant hemisphere (i.e., right hemisphere in right-handers and left hemisphere in left-handers). Here we studied the impact of such functional laterality on orientation constancy by measuring visual perception of upright with changes in lateral head position in 12 right handed and 12 left handed subjects. We used subjective visual vertical (SVV) to measure perception of upright before, during, and after prolonged lateral head tilts of 20° from upright position (~15min). Torsional eye position was also measured simultaneously using video oculography. The initial SVV error during the head

tilt was in the opposite direction of the head tilt (right handed mean: -2.6° right head tilt and 0.2° left head tilt; left handed mean: -5.0° right head tilt and 3.8° left head tilt), but there was a gradual drift in SVV responses in the direction of the head tilt (right handed mean: 0.2° right head tilt and -0.5° 1 left head tilt; left handed mean: 0.7° right head tilt and -0.5° left head tilt). After the head returned to upright position, there was also an SVV aftereffect in the direction of the previous head tilt (right handed mean: 2.6° right head tilt and -3.8° left head tilt; left handed mean: 1.6° right head tilt and -3.0° left head tilt). In both groups ocular torsion always drifted towards zero (the eye position during upright) by an average of about 4 degrees. These findings show the effects of hemispheric laterality and orientation constancy with respect to higher-order neural mechanisms that contribute to perception of upright and lower-order mechanisms that control torsional eye position.

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Poster

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Title: Rare variants in axonogenesis genes connect three families with sound-colour synaesthesia

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Abstract: Synaesthesia is an intriguing non-pathological neurological phenomenon where stimulation of one sense provokes an automatic and consistent secondary perception. Although the molecular mechanisms underlying synaesthesia are not yet known, affected people show altered structural and functional neural connectivity. The trait also appears to be more common amongst people with autism spectrum disorder (ASD) and savant abilities. Previous linkage studies searching for shared loci of large effect size across multiple families have had limited success. In this study, we applied whole exome sequencing to 3 multiplex families with sound-colour (auditory-visual) synaesthesia. Combined, we identified 37 rare genetic variants that perfectly followed the synaesthesia phenotype within a family. No variants or genes matched

across families, consistent with the emerging consensus that synaesthesia is a multigenic trait, prompting us to look for unifying pathways. Gene ontology enrichment analysis revealed a set of 6 genes associated with axonogenesis and cell migration, with the corresponding variants encompassing all 3 families. These genes — S*LIT2*, *MYO10*, *ROBO3*, *ITGA2*, *COL4A1*, and *SLC9A6* — are expressed in the human auditory and visual cortices throughout development, including early childhood when synaesthetic associations are formed and refined. To test whether these genes reflect neurological processes applicable to other families with sound > colour synaesthesia, we next identified genes with correlated developmental expression patterns. Amongst the 109 coexpressed genes, 5 fell within putative synaesthesia linkage peaks, suggesting axonogenesis as a shared pathway implicated in a proportion of people with this form of synaesthesia. These results provide the first gene-level support for hyperconnectivity in the aetiology of synaesthesia, and identify an entry point for molecular approaches to the neurobiology that delineates our sensory experiences.

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Poster

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Support: Japanese Grant-in-Aid for Scientific Research(C)-17K07046

Title: The simple material discrimination task examined haptic evaluations of material objects in human and possibly nonhuman primate subjects

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Abstract: Materials of surface provides a powerful clues to object recognition. Although such material perception is strongly dependent on perceiving both visual texture information and haptic information, material perception is not well understood in model animals for physiological studies. While we have trained two monkeys with a material discrimination task, we here examined human subjects by means of the similar task for comparison. Five human subjects (3 male and 2 females, age 21-57) reported four haptic-scores (rough/smooth, hard/soft, hot/cold or dry/wet) in five steps for a set of 109 material samples. They also reported five material-scores, indicating resemblance to each reference material (metal, wood, carpet, soft-gel-sheet, and urethane-foam). Relative scores were used for classifying sample materials into five material categories. They evaluated these scores by touching these samples under blind conditions or with

only visual inspection under room light. Order of sample presentation was randomized and each sample was presented once in a daily session. (1)The principle component analysis was applied to the haptic scores. In the two dimensional feature space of the first and second components (contribution rate; 50.0% and 32.6%), data were distributed over the wide area, indicating wide variety of the sample set. Top 20% samples for each haptic-score were well localized in this space. Similarly, samples with high material-scores (>4.0) were well localized in the same feature space. (2)Multiple regression analysis indicated that the four haptic-scores, especially those of hard/soft and hot/cold, were well predicted by the linear regression due to the material-scores ($p<0.01$). (3)To compare the results among individual subjects and experimental conditions, we modified the multidimensional scaling analysis, so that the four reference materials were presented at the fixed locations in two dimensional space. Individual difference was small enough to preserve the material categorization due the material-scores (three-way ANOVA, $p<0.01$). By visual inspection, scores tend to form a compact cluster for each material categories. However, the difference between materials was still preserved within each material category. Therefore, the relatively simple material discrimination task was sufficient for evaluating material perception within and between the material categories in a reliable manner. Since the material-scores can be acquired by a behavioral task, haptic perception might be evaluated even in primate subjects by using the similar material discrimination task.

Disclosures: M. Ito: None. **A. Tsuzura:** None. **M. Sasaki:** None. **F. Hamano:** None. **K. Mitsuhashi:** None.

Poster

688. Cross-Modal Processing: Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 688.08/HH24

Topic: D.10. Multisensory Integration

Title: Synesthetes produce different language in creative writing tasks

Authors: *R. MORALES[1], S. LUNDQVIST[2], T. DOTY[2], D. LARRANAGA[2], R. B. ESQUENAZI[3], A. RUTCHICK[5], S. A. DREW[4]
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Abstract: A condition known as synesthesia is commonly characterized by multiple sensory perceptions elicited by a single stimulus. These percepts can be intramodal (e.g. grapheme-color) or intermodal (e.g. lexical- gustatory). Aim: This exploratory research implements elements of both social and perceptual psychology to evaluate differences in synesthetes compared to controls in components of language production. In this study we observed trends in lexical

descriptors used by participants who experience synesthtetic perceptions compared to those who do not experience this condition. There appear to be multiple markers in which synesthetes significantly differ from controls. Method: Survey data of synesthetic perceptions and writing samples were collected. Writing tasks consisted of describing a picture, telling a story given three prompt words, describing a childhood memory, and recall of a recent or memorable dream. Results: Analysis of 180 participants' writing profiles was conducted using LIWC 2015 software (Pennebaker et al. 2015), an automated text analysis program that evaluates linguistic elements of writing samples. Findings indicate distinct differences between synesthetes and non-synesthetes, in the dimension of perceptual processing words (i.e. see, hear, feel, percept) with the strength of differences varying across tasks.

Disclosures: R. Morales: None. **S. Lundqvist:** None. **T. Doty:** None. **D. Larranaga:** None. **R.B. Esquenazi:** None. **A. Rutchick:** None. **S.A. Drew:** None.

Poster

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Topic: D.10. Multisensory Integration

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BT/RLF/Re-entry/31/2011

BT/07/IYBA/2013

National Brain Research Centre core funds

Title: Biophysically realistic neuronal model explains the inter-individual differences in the processing of multisensory speech

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Abstract: In a predominantly used paradigm of speech perception (McGurk effect), participants perceive illusory speech sound (crossmodal) when presented with incongruent audio-visual (AV) stimuli. However, a large number of participants rarely perceive the illusion. Notably, existing studies in the field primarily accentuate the correlation between subjective behavior and cortical activations to reveal the neuronal mechanisms. Nonetheless, this approach does not provide mechanistic explanation of the inter-individual differences. In the present study, we explain our empirical observations of large-scale functional brain networks underlying crossmodal perception employing biophysically realistic neuronal models. Importantly, we propose how

coupling between the key neuronal systems can explain the observed changes in functional connectivity pattern dynamics between frequent and rare perceivers of McGurk effect.
EEG data was collected from 35 healthy volunteers who signed informed consents, approved by the Institutional Human Ethics Committee of National Brain Research Centre, India. The participants reported their percept while watching a set of incongruent and congruent AV stimuli. Based on their behavioral responses, the participants were categorized as frequent and rare perceivers of the McGurk illusion. Global coherence was computed from sensor-level EEG data to study the dynamics of the cortical network following crossmodal perception. Subsequently, a network of excitatory and inhibitory Hindmarsh-Rose neurons were used to represent a cortical area. Different time constants were used in the network to distinguish between auditory (fast), visual (slow) and multisensory (intermediate) areas. Subsequently, coherence spectras were computed from simulated large-scale network dynamics.
Frequent perceivers exhibited an enhanced gamma band coherence accompanied by decreased alpha and beta band coherence during crossmodal perception. For rare perceivers crossmodal perception was characterized with decreased alpha coherence. Our neuronal model could exhibit a coherence pattern similar to frequent perceivers when the direct coupling between the auditory and visual nodes was increased. Furthermore, an increase in the coupling between the auditory and the multisensory node could qualitatively generate the coherence pattern of the rare perceivers. Thus we predict the dynamic interplay between a fast temporal processing system (e.g. auditory) and slow temporal processing system (e.g. visual, multisensory) is the most crucial factor for crossmodal perception.

Disclosures: V.G. Kumar: None. **S. Dutta:** None. **D. Roy:** None. **A. Banerjee:** None.

Poster

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Support: the Natural Sciences and Engineering Research Council (NSERC)

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Title: Effects of audio and text messages on avoidance strategies while walking in healthy young adults

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Abstract: Texting while walking poses a serious threat to safe locomotion, as multi-tasking can over-burden perceptual-cognitive resources that are essential for obstacle detection and avoidance. In this study, we tested the hypothesis that audio processing is less disruptive than visual processing for obstacle circumvention, as locomotion relies heavily on visual inputs. We expected audio messages to induce smaller alterations in avoidance strategies compared to visual (written) text messages. Healthy, right-handed adults (n = 7, 57% male, aged 25 ± 2 years (mean ±1SD)) were tested while walking over ground and viewing a virtual environment (VE) displayed in a helmet mounted display. The VE simulated a subway station with a target 11m straight ahead. Three non-reactive female avatars were positioned 7m ahead of the participant (±40° right/left and straight ahead at 0°). As the walking subject reached 0.5m of forward displacement, one of the 3 avatars would randomly approach while the others walked away. A collision would occur at 3.5m along the midline if the subject continued to walk straight with no avoidance. Message conditions that were tested included a visual text message, an audio message and no message. When present, messages were delivered at 0.5m of forward displacement (onset of avatar movement). The ability of the subjects to avoid the approaching avatar was characterized using the 3D position and orientation of the head recorded with a 12-camera Vicon system. Only two collisions occurred out of a total of 420 recorded trials, one for each message modality. For non-collision trials, when compared to the no message condition, visual text messages induced slower average and minimal walking speed and a wider deviation of the walking trajectory. In contrast, audio messages led to an increase in average and minimal walking speed but no significant change in maximal trajectory deviation. No consistent changes in the minimum distance maintained from the obstacle and the onset time of avoidance strategies were observed across tested conditions. We thus conclude that attending to phone messages while walking modifies obstacle avoidance strategies. As hypothesized, visual text messages cause greater dual-task interference compared with the auditory modality, as evidenced by the trend of reduced walking speeds and larger deviations in response to reading. While the use of larger trajectory deviations with visual text messages may reflect an underlying ‘safer’ avoidance strategy, it may pose further risk for possible collisions in the presence of multiple pedestrians. Audio messages may thus be considered as a safe alternative for on-the-go communication while walking.

Disclosures: W.H. De Souza Silva: None. **J. Fung:** None. **B.J. McFadyen:** None. **A. Lamontagne:** None.

Poster

688. Cross-Modal Processing: Humans

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Program#/Poster#: 688.11/HH27

Topic: D.10. Multisensory Integration

Support: NIH Grant 409670

Title: Cross-modal interactions in motion perception in blind adults

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Abstract: In sighted humans, there is evidence to support the notion of directional selectivity within the human middle temporal complex for visual motion information (Huk, Dougherty, & Heeger, 2002; Koyama et al., 2005; Morrone et al., 2000; Tootell, Mendola, Hadjikhani, Liu, & Dale, 1998). It has been shown that distinct regions within the motion-sensitive human middle temporal complex (hMT+) respond to radial and translational motion, suggesting a functional specialization within hMT+ for processing different types of motion information (Morrone et al., 2000). Furthermore, previous studies have found that the direction of moving sounds can be reliably decoded from fMRI activation patterns within putative hMT+ in blind adults (Dormal, Rezk, Yakobov, Lepore, & Collignon, 2016; Wolbers, Zahorik, & Giudice, 2011). The aim of this study is to elucidate the functional specialization of hMT+ in response to different auditory and tactile motion directions using fMRI. Moreover, this study will assess how combining auditory and tactile motion cues modulate BOLD responses in comparison to either tactile or auditory cues alone. Two groups are assessed, early blind and matched sighted controls. Auditory and tactile motion cues with different directions of motion are used to evaluate the functional specialization of the hMT+ region in both groups. In addition, the effect of combining tactile and auditory motion information using different levels of motion coherence is used to measure modulations in the BOLD response to multisensory motion inputs. These results not only elucidate the functional specialization of putative visual cortical areas in blind individuals, but also contribute to our understanding of how perception in the sensory-deprived brain may be enhanced via multisensory inputs.

Disclosures: M.M. Barrett: None. **J.P. Rauschecker:** None.

Poster

688. Cross-Modal Processing: Humans

Location: Halls A-C

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Program#/Poster#: 688.12/HH28

Topic: D.10. Multisensory Integration

Title: Impaired development of audiovisual integration in autism and the effects of modality switching

Authors: *M. J. CROSSE[1], J. J. FOXE[3], S. MOLHOLM[2]
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Abstract: Simultaneous presentation of information from different sensory modalities often leads to faster responses than presenting the same information separately. Response times for multisensory stimuli have been shown to exceed what would be predicted if the faster of the two unisensory responses were to win out (i.e., the race model; Miller, 1982), indicating integrated processing of the individual sensory streams. This ability to benefit from multisensory inputs increases across middle childhood and adolescence (Brandwein et al., 2011). However, the developmental course of the audiovisual (AV) facilitation that is observed in typically developing (TD) children is not seen in those with an autism spectrum disorder (ASD; Brandwein et al, 2012). Using the same audiovisual speeded reaction time (AVSRT) task, and data from nearly 300 participants ranging in age from 5 to 45, we demonstrate that this development is delayed until adolescence in ASD participants, but recovers considerably in adulthood. However, ongoing work has recently revealed that mixed presentation of unisensory and multisensory stimuli may give rise to the apparent redundant target effect because of a behavioral cost to switching modality during the unisensory trials, but not the multisensory trials. We therefore separated trials into those preceded by a different stimulus (switch trials) and those preceded by the same stimulus (repeat trials). Our analysis demonstrates that both TD and ASD participants show a "switching cost", but that only the TD participants show race model violation on the repeat trials. This violation may be due to a residual "mixing cost" because participants are still required to attend across modalities on a repeat trial. The fact that this mixing cost differentially affects behavior in TD and ASD participants suggests that it may in part reflect an underlying deficit in deployment of crossmodal attention. To further investigate these behavioral differences, we also examine neural responses to the switch and repeat trials recorded using high-density electrophysiology (EEG).

Disclosures: M.J. Crosse: None. **J.J. Foxe:** None. **S. Molholm:** None.

Poster

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Topic: D.10. Multisensory Integration

Support: KAKENHI 26120002

KAKENHI 25350776

KAKENHI 17K01682

Title: Movement back projection during observation of an illusory embodied hand: Evidence by EEG mu-rhythm

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Abstract: We normally experience that our body is our own, and a coherent and unified entity separate from the external world. This sense of body ownership is fundamental to self-consciousness. However, people can also experience body ownership over a non-corporal object using a rubber hand illusion (RHI), wherein participants perceive a fake hand as their own by stroking their hidden real hand and the visible fake hand simultaneously (i.e., embodiment of the fake hand). Several RHI studies have reported that visual manipulation of the fake hand was back projected onto perception in the real hand (e.g., thermal or pain sensitivity). In this study, we examined whether motor manipulation of the embodied fake hand similarly back projected onto the observer's motor system by a combination of a novel RHI paradigm and electroencephalography (EEG). Eighteen healthy volunteers participated in the experiment. An experimenter stroked participants' and the false hands in synchrony (synchronous condition) or in asynchrony (asynchronous condition). Stroking was sometimes interrupted by unexpected movement of the false hand (i.e., finger spreading). Brain activities during the task were investigated using EEG. As a measure of motor system activation, we analyzed decrease of frequency power in a mu rhythm band (8-13 Hz; mu-suppression) during action observation. Subjective reports using a questionnaire indicated that participants perceived illusory body ownership of the false hand in the synchronous condition but not in the asynchronous one. Participants' fingers of the stroked hand moved spontaneously during action observation. The incidence of finger movements was significantly higher in the synchronous condition and also increased as a function of trials. EEG data showed greater and longer mu-suppression in the synchronous condition compared to the asynchronous one. Additionally, we found that the stronger the feeling of body ownership over the false hand, the greater the mu-suppression in the motor system. These findings provide strong behavioral and neurophysiological evidence of motor back projection, in which the movement of an illusory embodied 'body part' is inversely transferred to the sensorimotor system of the observer.

Disclosures: S. Unenaka: None. **S. Shibuya:** None. **T. Zama:** None. **S. Shimada:** None. **Y. Ohki:** None.

Poster

688. Cross-Modal Processing: Humans

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Topic: D.10. Multisensory Integration

Title: Hearing loss modulates auditory cortex response to audio-visual speech

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Abstract: Previous research provides compelling evidence for a cross-modal reorganization in the auditory cortex following auditory sensory deprivation, leading to increased neural responses to visual input. Recently, it was shown that these changes may already occur after a moderate hearing-impairment and not only after severe hearing-loss. By using functional magnetic resonance imaging, we investigated the influence of mild to moderate hearing-impairment on audio-visual speech processing.
We here measured 20 hearing-impaired participants (63.5 ± 5.4 years) with mild to moderate high-frequency hearing-loss who were not wearing a hearing-aid yet and 19 normal-hearing participants (63.2 ± 5 years). The fMRI paradigm consisted of an audio-visual speech detection task in which the participants had to indicate which word was included in the previous sentence. Sentences were presented either audio-visually congruent, audio-visually incongruent, only visually or only auditory. Loudness was individually adjusted to 80% speech intelligibility to enable equal performance in both groups. Outside the MRI, participants performed the McGurk illusion as a measure for audio-visual integration.
Our main aim was to relate high-frequency hearing loss to BOLD response amplitudes elicited by audiovisual speech processing. We observed a significant difference in BOLD response amplitudes for incongruent versus congruent input between hearing-impaired and normal-hearing subjects. Furthermore, the BOLD signal significantly correlated with hearing loss, with higher hearing-loss leading to an increased BOLD signal in the primary auditory cortex. Behaviorally we found a benefit of congruent audio-visual input and a distraction by incongruent audio-visual input, which was similar in both groups and did not correlate with hearing loss. Hearing loss, however, correlated with audio-visual integration in the McGurk task, with higher hearing-loss leading to stronger audio-visual integration.
Our data provide evidence for hearing-loss related changes in BOLD amplitudes in the auditory cortex. In line with previous research that hearing-impaired subjects tend to rely more on the visual input in challenging listening conditions, we here show a hearing-loss induced modulation of the BOLD response during incongruent audio-visual input. Behavioral measures showing an increased audio-visual integration with increasing hearing-loss complement our findings. These results suggest that cross-modal reorganization occurs early in the course of hearing loss and not only after severe hearing impairment, which may lead to an altered audio-visual speech processing.

Disclosures: S. Rosemann: None. **C.M. Thiel:** None.

Poster

688. Cross-Modal Processing: Humans

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Topic: D.10. Multisensory Integration

Support: National Research Foundation of Korea (NRF-2016R1C1B2016039)

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KAIST (Venture Research Program for Graduate and PhD Students)

Title: Systematic influence of the auditory system on human visual perception

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Abstract: Sensory information of different modalities is known to be merged in higher cortical regions (Beauchamp, et al., 2004), but little is known about how the different sensory systems affect each other's information processing. Interestingly, a recent fMRI study reported that the activity induced by different stimuli of one sensory modality is discernable in non-pertinent sensory systems in human (Liang, et al., 2013); However, how such influence between different sensory systems is organized in humans remains a question.
In the present study, we hypothesized that the auditory system systematically affects information processing in the visual system. To test our hypothesis, we conducted a set of psychophysical experiments: Human subjects were briefly shown a Gabor filter with various orientations on the monitor screen while keeping their eyes at the center. Shortly before a visual stimulus appeared, either no acoustic stimulus or a sound of various frequencies was introduced. Then, subjects were instructed to rotate the test Gabor probe and match its orientation as accurately as possible to that of the visual stimulus presented; the error—the angular difference between the appeared stimulus and subjects' response—was used as the performance measure.
As a result, we found that acoustic stimuli of different frequencies significantly changed subjects' performance error compared to that under no-sound condition. These effects were not uniform across the visual space: visual perception at different visual locations were specifically affected by sound frequencies within a given range, and such frequency bandwidth gradually shifted across the visual space.
Our results indicate that the auditory influence on visual perception is systematically organized. Because the information that the auditory and visual stimuli carry start to be processed in the very early stages of the sensory systems, we suggest that the systematic matching between the audio-visual systems originates from the early sensory cortices.

Disclosures: **J. Song:** None. **S. Paik:** None.

Poster

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Topic: D.10. Multisensory Integration

Support: NIH Grant 5R01EY015545-12

Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech

Title: Mirroring the feeling of touch in the activity of single neurons in human posterior parietal cortex

Authors: *C. Y. ZHANG[1], T. AFLALO[1], D. OUELLETTE[2], E. R. ROSARIO[2], N. POURATIAN[3], R. A. ANDERSEN[1]
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Abstract: The motor mirror system has been extensively studied, with fMRI and single-unit studies finding regions of cortex activated both when performing an action and also when observing someone else performing the same action. A complementary, but less thoroughly investigated system, is the sensory mirror system, where some regions of cortex are activated both when feeling a sensation of being touched and also when observing someone else being touched. Here we tested for the presence of a sensory mirror system within a 4 by 4 mm patch of anterior intraparietal area (AIP) of posterior parietal cortex (PPC) of a tetraplegic participant (NS) participating in a brain-machine interface clinical trial. We studied neural responses when NS either felt a touch on her face or shoulder (both sensations above the level of injury) or visually observed someone else's face or shoulder being touched. Sensory mirroring was observed at both the single-unit and population level. Activity for touching NS was observed regardless of whether NS's eyes were open or closed suggesting that the mirroring response was not purely visual in nature. Mirroring was also specific to body part. Comparing neural population level similarity measures, we found that the similarity between NS being touched on the face and observing someone else being touched on the face was significantly greater than the similarity between the face and shoulder. Likewise, similarity measures between when NS felt and observed touches of the shoulders were significantly greater than the similarity between the shoulder and face. Our results show for the first time at a single-unit and population level in humans that AIP contains a high level representation of the sensation of touch that is activated both when feeling a touch and observing someone else being touched.

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Poster

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Topic: D.10. Multisensory Integration

Title: Divisively normalized integration of visual and proprioceptive information for motor adaptation

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Abstract: When we experience an error during a movement, the motor system corrects the motor command according to the difference between predicted and actual sensory information. Although previous studies have investigated the contribution of visual and proprioceptive errors for the motor adaptation (Wei & Kording JNP 2009; Marko et al., JNP 2012), it has not been fully elucidated how the errors in the two distinct sensory modalities are integrated. Here, we aimed to clarify the way of integration by examining single-trial motor adaptation during a reaching task when various combinations of visual and proprioceptive errors were systematically imposed. Fourteen participants moved a cursor toward a front target with their unseen hand. We interleaved one of 35 types of perturbations: the combinations of directional errors of the cursor (±45°, ±30°, ±15°, 0°) (visual error: VE) and the hand (±30°, ±15°, 0°) (proprioceptive error: PE) around a start position with the error-clamped methods. In the subsequent reaching trial to the same front target, we measured lateral force to the channel as an index of the motor adaptation (aftereffect). The aftereffects were suppressed when the errors were imposed in the opposite direction (e.g., +30° VE and -15° PE), but they were not increased even when the error was added to another sensory modality (e.g., +15° PE did not increase the aftereffect to +30° VE). Thus, simple summation of the aftereffects obtained separately for each VE and PE could not predict the size of the aftereffect observed when both types of errors were simultaneously imposed. The idea of “relevance of error” (Wei & Kording, JNP 2009) or Bayesian integration model (Ernst & Banks, Nature 2002) could not explain our results: For example, even when the size of the error was increased with the relevance of error maintained (e.g., from +15° VE and PE to +30° VE and PE), the aftereffect did not increase. Alternatively, we assumed that the aftereffect is determined as a response to divisively normalized error information (Carandini & Heeger, Nat Rev Neurosci, 2012) and that this mechanism works as a way of integrating multisensory information (Oshiro et al, Nat Neurosci 2011). We found that this simple

mechanism could nicely reproduce the complicated pattern of aftereffects to combination of VE and PE. This result suggests that divisive normalization that is known to be a canonical neural computation is likely to work in the motor learning system.

Disclosures: **Y. Kato:** None. **T. Hayashi:** None. **D. Nozaki:** None.

Poster

688. Cross-Modal Processing: Humans

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Topic: D.10. Multisensory Integration

Support: SFB/A3

ERC-2010-AdG-269716

Title: Oscillatory activity underlying attentional modulation of crossmodal matching in a trimodal sensory paradigm

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Abstract: Crossmodal matching is a key mechanism underlying perceptual interaction in complex multisensory environments. That is, signals from distinct modalities can be integrated more effectively if they coincide in time and space, but also if structural or semantic features can be matched. When more than two modalities are involved, highly ambiguous situations can arise where attention is needed to resolve conflicts. Here, we used a novel multisensory paradigm featuring audio-visuo-tactile stimuli to investigate crossmodal matching of stimulus amplitude changes. In this paradigm, subjects had to focus on either visuo-tactile or audio-visual components of the trimodal stimulus for which crossmodal congruence of brief intensity changes had to be evaluated. The respective third component of the trimodal stimulus served as a task irrelevant distractor. Both stimulus-driven effects of crossmodal congruence and cognitive effects of selectively attending or ignoring stimulus components were evaluated. Behaviorally, visuo-tactile matching was faster than audio-visual matching. Moreover, crossmodal congruence led to faster reactions. While the latter corresponds to well documented findings on multisensory enhancement, the former indicates differences with respect to attentional aspects of crossmodal matching. In a source level analysis of EEG data, we found neither significant modulation of oscillatory power within nor coherence between early sensory regions involved in the task. In a whole-brain analysis of oscillatory power we observed that right central and frontal alpha power was decreased for visuo-tactile matching. Attended crossmodal congruence induced higher theta

power in cingulate and lower alpha power in parietal and frontal cortex. These preliminary results suggest that crossmodal matching and its modulation by attention do not occur at early sensory processing stages. Rather, both stimulus-driven (i.e., multisensory enhancement) and cognitive effects are reflected in modulation of higher cortical areas and, thus, suggest that crossmodal interaction in our task takes place rather late in the processing hierarchy. In an ongoing analysis of functional connectivity of the same dataset, we investigate changes in corticocortical coupling underlying crossmodal matching.

Disclosures: **J. Misselhorn:** None. **U. Friese:** None. **A.K. Engel:** None.

Poster

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Title: Alpha and beta oscillations in the language network, motor and visual cortex index semantic congruency between speech and gestures in clear and degraded speech

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Abstract: Oscillatory dynamics are thought to subserve the integration of information from multiple modalities. This is particularly relevant during face-to-face communication, which integrates auditory (e.g., speech) and visual inputs (e.g., gestures). Under adverse listening conditions, speech comprehension can be improved by the semantic information conveyed by these gestures. However, when gestures mismatch speech, audiovisual integration might be hindered, especially when speech is degraded and the semantic information from gestures cannot aid to resolve the remaining auditory cues. Here, we used MEG to investigate how oscillatory dynamics support the semantic integration of speech and iconic gestures in clear and degraded speech. Participants were presented with videos of an actress uttering an action verb, accompanied by a matching (e.g., a mixing gesture + 'mixing') or a mismatching gesture (e.g., a drinking gesture + 'walking'). Speech in the videos was presented clear or degraded by using 6-band noise-vocoding. Semantic congruency and speech degradation modulated oscillatory activity in the alpha (8-12 Hz) and beta (15-25 Hz) band. Source analyses revealed larger alpha and beta power suppression in LIFG and visual cortex when speech was accompanied by a mismatching as compared to a matching gesture, but only when speech was clear. This indicates

that the visual system is more engaged to allocate attention to mismatching than matching gestures when speech is clear. The observed congruency effects in the LIFG are likely to reflect an increased semantic processing load to resolve the conflict. This conflict reduced when speech is degraded, due to the lack of auditory cues. In clear, but not degraded speech, beta power was more suppressed in (pre)motor cortex when a gesture mismatched than matched the speech signal, suggesting that a listener might simulate the mismatching gesture to re-evaluate its fit to speech. Beta power was more suppressed in MTG/STG, MTL and AG when speech was degraded and gestures mismatched as compared to matched speech. This suggests that listeners try to resolve the speech signal, but that semantic audiovisual integration might be hindered when the mismatching gesture fails to aid retrieval of the degraded input. Our results provide novel insight by revealing how low-frequency oscillations support semantic audiovisual integration in clear and degraded speech: when gestures mismatch and speech is clear, listeners engage the extended language network to process the mismatching gesture. In degraded speech, the extended language network is less engaged, possibly reflecting the hindered coupling of gestures and the degraded signal.

Disclosures: **L. Drijvers:** None. **A. Ozyurek:** None. **O. Jensen:** None.

Poster

688. Cross-Modal Processing: Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 688.20/HH36

Topic: D.10. Multisensory Integration

Support: Natural Science Foundation of China (31371127)

Program for New Century Excellent Talents in the University of China (NCET-12-0645)

Chang Jiang Scholars Program (2016)

Title: Neural practice effect during cross-modal selective attention: General and modality-specific effects

Authors: X. JING, N. LIU, *Q. CHEN
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Abstract: Practice and experiences gradually modify the central nervous system, from the synaptic level to large-scale neural networks. However, the supra-modal and modality-specific effects of practice during cross-modal selective attention remain unknown. In two fMRI studies, we adopted a cross-modal interference paradigm in conjunction with the hybrid fMRI design. In alternating task blocks, participants attended to either the visual or the auditory component of

simultaneously presented audiovisual stimuli and ignored information from the unattended modality. The temporal position of each and every trial in a given block was included as a covariate to calculate how neural activity changed as a function of the time of practice. Results from the two fMRI studies consistently showed that with the progress of practice, neural activity linearly decreased in the frontoparietal central executive network (CEN) while increased in the default-mode network (DMN). Critically, the practice effect in CEN and DMN occurred independently of the modality attended, indicating the general mechanisms of selective attention. On the other hand, increasing extent of functional decoupling between the auditory and the visual systems was observed with the progress of practice and varied as a function of the modality attended. During auditory attention, the auditory system was functionally decoupled with both the dorsal and ventral visual stream with the practice; during visual attention, the auditory system was decoupled only with the ventral visual stream. Taken together, both supra-modal mechanisms in CEN and DMN and modality-specific mechanisms in the sensory systems associated with practice were revealed during cross-modal selective attention.

Disclosures: X. Jing: None. **N. Liu:** None. **Q. Chen:** None.

Poster

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Topic: D.10. Multisensory Integration

Support: National Institute of Health Center Grant U54 HD083211

CTSA Award KL2TR000446

Title: Temporal facilitation of audiovisual speech processing in young children with and without autism spectrum disorder

Authors: *T. G. WOYNAROSKI[1], D. M. SIMON[2], J. I. FELDMAN[2], S. EDMUNDS[4], A. TU[2], W. KUANG[2], J. G. CONRAD[2], P. SANTAPURAM[2], M. T. WALLACE[3]
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Abstract: Explaining individual differences in language understanding and use of young children with autism spectrum disorder (ASD) is a top priority of research because language has been repeatedly linked with long-term outcomes in this population. Temporal facilitation (the gain in speech processing speed that is associated with having access to visual speech cues) may account for variability in language understanding and use across children with ASD. Previous work indicates that older, relatively high functioning children with ASD are highly variable in

their ability to perceive visual speech cues. Children with ASD who do not use visual speech cues may process speech more slowly, and slow speech processing may underlie impairments in understanding language, leading to delays in using language. This project will evaluate the theoretical association between temporal facilitation and language in a sample of children with ASD who are younger and who represent a broader range of cognitive and functioning levels than have previously been studied. Our task is a direct neural measure that is low in demand, but that has the temporal resolution needed to capture the speed of the neural response to rapid audiovisual speech input - event-related potentials (ERPs). We hypothesize that young children with ASD will show less temporal facilitation on average relative to their typically developing peers, but that there will be a wide range of individual differences in the extent to which visual cues "speed up" speech processing across children with ASD. We anticipate that the degree of temporal facilitation experienced (a) may be explained by gaze patterns to audiovisual speech and (b) will positively correlate with measures of language understanding and use. IMPACT: If our hypotheses are born out, this work will have identified an impediment to language development in children with ASD that independent evidence suggests is malleable and therefore potentially remediable.

Disclosures: **T.G. Woynaroski:** A. Employment/Salary (full or part-time):; Vanderbilt University Medical Center. **D.M. Simon:** None. **J.I. Feldman:** None. **S. Edmunds:** None. **A. Tu:** None. **W. Kuang:** None. **J.G. Conrad:** None. **P. Santapuram:** None. **M.T. Wallace:** A. Employment/Salary (full or part-time):; Vanderbilt University.

Poster

688. Cross-Modal Processing: Humans

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Topic: D.10. Multisensory Integration

Support: NIH Grant EY019924-08

Research to Prevent Blindness/Lions Club International Foundation

Title: Audio-visual cross-modal processing in individuals with cortical/cerebral visual impairment

Authors: *E. BAILIN[1], C. R. BENNETT[2], M. REZK[3], O. COLLIGNON[3], L. MERABET[4], C. M. BAUER[1]
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Abstract: Cortical/Cerebral Visual Impairment (CVI) is caused by early developmental brain damage and is the leading cause of pediatric visual impairment in developed countries (Good et al. 2001 and Dutton 2013). Despite its prevalence and breadth of associated visual dysfunctions, very little is known regarding multi-modal processing in children with CVI. To this end, the current study utilized functional MRI (fMRI) to determine how adolescents with CVI process auditory and visual cross-modal motion.

A cohort of individuals with CVI (ages 14-24, mean= 18.4) and normally-sighted and developed controls (ages 15-25, mean 19.75) underwent our neuroimaging protocol on a 3T Philips Achieva system using a 32-channel phased array head coil. A T1w structural scan, a field map, and two fMRI experiments (totaling 6 runs) were acquired for each subject. During the first experiment, blocks of horizontal visual movement, horizontal auditory noise, static images, and random auditory noise were interspersed with rest blocks. During the second experiment, subjects were presented with blocks of auditory and visual motion that were either moving in the same (congruent) or in opposite (incongruent) directions, which were interspersed with blocks of static stimuli and rest. The primary contrast of interest was congruent vs. incongruent motion in areas V1, A1, and hMT+, which were functionally defined from experiment one. Functional data were preprocessed in FSL using standard processing pipelines including brain extraction, MNI registration, and motion correction. A GLM using FLAME 1+2 was used to assess cluster-wise significance between groups, focusing on A1, V1, and hMT+. Significance was set at z 2.3, $p < 0.05$.

Compared to controls, the CVI group showed significant bilateral decreases in activation in areas V1 and hMT+, and in the left A1, with significant increases in activation in right A1 during both visual and auditory uni-modal motion, as well as congruent and incongruent cross-modal conditions compared to rest. Compared to controls, the CVI group also showed bilateral increases in A1, V1, and hMT+ when comparing congruent and incongruent conditions, however these were stronger in the right hemisphere.

Together, these results indicate that individuals with CVI show significantly different patterns of activation compared to controls during both uni- and cross-modal processing of auditory and visual motion stimuli. Thus suggests that individuals with CVI may require greater amounts of neural resources to process visual and auditory motion and that visual motion may be particularly affected

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Poster

688. Cross-Modal Processing: Humans

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Program#/Poster#: 688.23/II3

Topic: D.10. Multisensory Integration

Support: Deutsche Forschungsgemeinschaft GRK 1589/2

Title: The Ganzfeld experience: Characterizing multimodal integration failure using resting-state fMRI

Authors: N. JAGANNATHAN[1], M. LJUBLJANAC[1], T. NIERHAUS[2], *T. SCHMIDT[1,2]
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Abstract: The Bayesian brain hypothesis posits that interactions between top-down predictions and bottom-up sensory signals modulate perception, such that disruptions in the balance between the two processing streams can result in multimodal integration failure. This phenomenon can be tested using multimodal Ganzfeld (MMGF), a sensory homogenization technique in which the visual and auditory systems are exposed to totally unstructured stimulation (i.e. homogenized visual input and auditory white noise). Sustained exposure to MMGF can cause alterations in consciousness that are characterized by pseudo-hallucinatory experiences. We used resting-state fMRI to identify how changes in functional connectivity between the thalamus, sensory, and higher-order brain networks characterize these integration failures. Data from N=19 subjects were acquired in a 25min MMGF functional scan, preceded and succeeded by 7min control scans. The phenomenology of the MMGF-induced altered state of consciousness was retrospectively assessed using the Altered States of Consciousness Rating Scale and Phenomenology of Consciousness Inventory. The psychometric assessments demonstrated that the homogenization of sensory inputs used in MMGF induces substantial deviation from the normal wakeful state. A comparison of the MMGF condition to the pre- and post- control sessions revealed increased Eigenvector centrality for the precuneus during the Ganzfeld experience. Furthermore, a progressive decoupling of sensory regions from the thalamus was observed under sustained exposure to MMGF. In line with the predictive coding framework, the increased Eigenvector centrality in the precuneus may reflect increased top-down influences. Additionally, the reduction in functional connectivity between the thalamus and lower-order sensory regions is indicative of disturbed bottom-up signaling. This imbalance of top-down and bottom-up processing reflects multimodal integration failure, which in turn gives rise to the alterations in consciousness characteristic of the Ganzfeld experience.

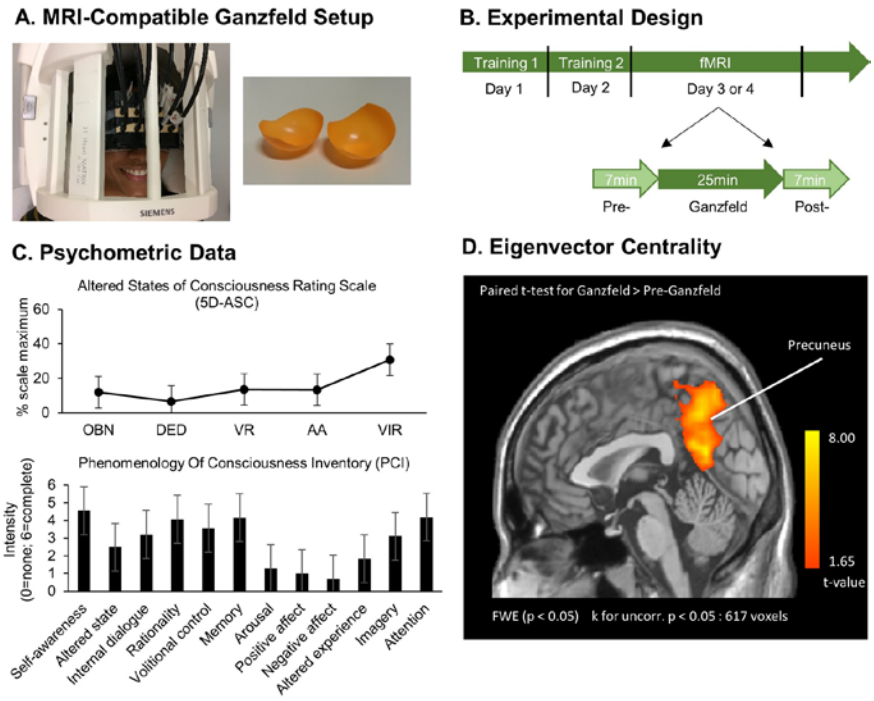

Figure 1. Experimental paradigm and results. **A. MMGF setup:** anatomically-cut ping pong balls (right) and customized goggles with fiber optic cables (left) were used to provide homogenized visual input during the MMGF. **B. MMGF sessions:** subjects completed two training sessions prior to participating in the pre-, Ganzfeld, and post- resting-state scans. **C. Questionnaires:** average ratings across subjects are displayed for the 5D-ASC (OBN: Oceanic Boundlessness, DED: Dread of Ego Dissolution, VR: Visual Restructuralization, AA: Auditory Alterations, VIR: Vigilance Reduction) and PCI. **D. Eigenvector centrality:** increased centrality during the MMGF condition was observed for the precuneus, a core aspect of the default mode network.

Disclosures: N. Jagannathan: None. **M. Ljubljanac:** None. **T. Nierhaus:** None. **T. Schmidt:** None.

Poster

688. Cross-Modal Processing: Humans

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 688.24/II4

Topic: D.10. Multisensory Integration

Title: Visual and auditory cues can enhance subliminal tactile sensitivity but interfere with suprathreshold performance

Authors: *M. F. WESNER, E. LO, K. D. MACLAM, V. B. K. JOHNSON
Psychology, Lakehead Univ., Thunder Bay, ON, Canada

Abstract: Although cortical parcellation demonstrates localized functionality, there can be extensive underlying neural circuits that interconnect throughout associative and subcortical brain. Sometimes these interconnections can be preserved after neurological damage allowing patients to use intact, multisensory circuits for rehabilitation. Hierarchical integrative

efficiencies, however, are not well understood. Typically in multisensory research, response times (RTs) are measured while presenting coincidental stimuli across modalities. The problem is that RTs are based on high-threshold theoretical principles and do not account for integrative phenomena specific to hierarchical processing.
We psychophysically measured percent correct (%C) right-hand finger responses to haptic toe stimulations on the left foot. Fifty-seven participants (n=36 female, age 18 to 35) were screened for confounding medical conditions, and all had normal, or corrected-to-normal near acuity and auditory functioning. Using six von Frey monofilaments of varying target buckling forces (0.008 to 300 gm; log iterations), we presented the monofilaments to the tops of the second or fourth toe in a two-alternative forced choice experiment. Two experiments were conducted in which either a visual icon or a single frequency tone was presented simultaneously with the haptic presentations. Within each experiment, three conditions were used: (1) Control condition where the von Frey hairs were applied alone, (2) 100-percent cue condition where the cues correctly identified which of two toes were being tactually stimulated, and (3) 60-percent cue condition where the cues were only 60 percent valid. Cues were delivered for 350ms within the averaged 1.5 s haptic-delivery trial. Plotting %C as a function of log target force, we found a significant interaction ($p<.001$) between the Control and 60-percent cue validity measures, where detectability for subthreshold forces increased with the cues, but decreased at suprathreshold levels. For the 100-percent valid condition, all intensities showed near perfect detection, better than even the most intense tactile stimulus, indicating that participants disregarded all tactile presentations and used only the attention cues.
This systematic investigation reveals an important dependency on intensity and cue validity when it comes to integration and demonstrates how individuals may make selective multimodal, top-down decisions to optimize their volitional responses. Understanding these effects can play a prominent role in the development of more effective therapeutic training techniques for the neurologically impaired.

Disclosures: **M.F. Wesner:** None. **E. Lo:** None. **K.D. MacLam:** None. **V.B.K. Johnson:** None.

Poster

688. Cross-Modal Processing: Humans

Location: Halls A-C

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Program#/Poster#: 688.25/II5

Topic: D.10. Multisensory Integration

Title: Synesthesia and creativity: Looking at association with writing and word tasks

Authors: *T. DOTY[1], R. B. ESQUENAZI[2], D. L. LARRANAGA[3], A. RUTCHICK[4], S. A. DREW[5]

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Abstract: Synesthesia is a condition in which individuals experience an additional sensory stimulation automatically when exposed to particular stimuli. Research has shown that those with synesthesia tend to exhibit more creativity through art, music, and verbal tasks (Ward et al., 2008; Domino, 2009; Sitton & Pierce, 2004). Little research exists however examining quantitative examination of creativity and synesthetic percepts. This study examined the potential relationship between synesthesia and creativity, specifically in word and writing tasks. The participants completed a survey administered through MTURK, consisting of synesthesia screening questions, two implicit Remote Association Test (RAT) writing tasks, fifteen explicit RATs, and the same synesthesia screening questions to solidify consistency. The RATs consisted of word triads where one key word would fit with the three words individually. For example, the triad “cheese, baby, and moon” would be solved with the word “blue” to create the word pairs “blue cheese”, “baby blue”, and “blue moon”. In the implicit writing tasks, the instructions were to create a story using the triad words provided. To correctly “solve” the task, the participant must have used the answer word in their story. These stories were also assessed for creativity, such as figurative language. Figurative language was operationalized as language that is not interpreted in the literal sense, such as metaphors and hyperboles. The explicit RATs consisted of a word triad where the participants must supply the key word directly. No significant relationship was observed between synesthesia and either the implicit or explicit RATs. However, there was a significant association between the use of figurative language and synesthesia, providing quantitative support for a relationship between synesthesia and creativity.

Disclosures: R.B. Esquenazi: None. **D.L. Larranaga:** None. **A. Rutchick:** None. **S.A. Drew:** None.

Poster

688. Cross-Modal Processing: Humans

Location: Halls A-C

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Program#/Poster#: 688.26/II6

Topic: D.10. Multisensory Integration

Title: Relief from intractable phantom pain by combining psilocybin and mirror visual feedback (MVF)

Authors: *V. S. RAMACHANDRAN[1], C. CHUNHARAS[1,2], Z. J. MARCUS[1]
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Abstract: Patient AL sustained a compound fracture of the right tibia and 3 nails were inserted into the foot and tibia to stabilize them, promote healing, and avoid amputation. Four weeks later, his right leg amputated below the knee, and he was seen by us 2 weeks after amputation - with phantom pain (PLP) as the presenting complaint. From simple tests done on a lower-limb amputee, AL, we were able to demonstrate several new principles of brain organization, especially pertaining to the plasticity of connections and inter-modular interactions. We observed: 1) First we replicated our own previous finding that when an amputee watches someone else limb being touched stroked or tapped - he will experience these sensations as emerging from corresponding locations on the phantom. This inter-subject synesthesia results from activation of mirror neurons, leading to “I-her” confusion and misattribution of quale` from others to oneself. Viewing a leg massage applied to the volunteer V resulted in a massage being felting the phantom-sometimes relieving phantom pain. 2) Mirror visual feedback (MVF) produced some relief from pain as did, “phantom massage”, merely watching his friend massaging her own leg. 3) Intriguingly, when small doses of psilocybin were combined with the mirror he noticed a strong synergistic effect and after 2 weeks there was a complete elimination of PLP and reduction in paroxysmal episodes, so he was able to substantially reduce the dose of psilocybin. A dose response curve was obtained informally, and it was found that the relief was proportionate to the drug dose, suggesting a specific pharmacological effect. 4) Touching the precise location in the volunteer's leg, where the three nails were originally placed evoked a highly specific nail-like sensation boring through the leg even though neither leg nor nail existed. Using a joke shop “telescoping” nail, we created the visual illusion of a nail being pulled out - and AL reported corresponding pain relief. 5) Phantom fire from a Halloween shop - when lit in the vicinity of the phantom - produced warmth in the phantom. “It feels wonderful on my cramp”... “like lying next to a fireplace”, he cried. Taken collectively, these observations entail a radical revision. Brain modules are in a state of dynamic equilibrium with sensory inputs (vision modulates pain), the skin and bones (as in RSD/CRPS2), and even with other brains - so that someone else's massage is felt in your hand.

Disclosures: V.S. Ramachandran: None. **C. Chunharas:** None. **Z.J. Marcus:** None.

Poster

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Topic: D.10. Multisensory Integration

Support: KAKENHI Basic Research (A) (25240019)

KAKENHI Innovative Areas (16H01610)

Title: Two different phase coding mechanisms for integrating audio-visual information via slow neural oscillation

Authors: *H. MIZUHARA, T. KUMAGAI, A. OOZONO
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Abstract: Our sensory modalities simultaneously process a variety of information (e.g., visual and auditory information) throughout daily life. Our brain must appropriately bind relevant information into a coherent whole to segregate one object from others. How does the brain choose and bind relevant information from many inputs? Neural oscillation is a possible underlying mechanism that can answer this question. Namely, phase coding—where information can be integrated when arriving simultaneously at the same phase of neural oscillation—might be a functional role of neural oscillation. Two neural mechanisms (phase shift and amplitude suppression of neural oscillation) were considered as candidates to achieve phase coding via neural oscillation (Jensen et al., Trends Neurosci 2014). To test whether multimodal information is integrated by the phase coding via neural oscillation, we measured human scalp EEG during two audio-visual integration tasks: a ventriloquism task and a McGurk task. In the ventriloquism task, participants (4 females and 10 males) were required to judge sound location, with visual cues appearing prior to a sound stimulus to suggest/fake the sound location to which participants paid attention (Kumagai & Mizuhara, NeuroReport 2016). The visual cue used two conditions to induce bottom-up attention or top-down attention. The results showed that the bottom-up visual cue shifted theta oscillation phase, while the top-down cue suppressed alpha oscillation amplitude at electrode positions in the contralateral hemifield to which attention was paid. To confirm whether the phase shift manipulated the timing of neural excitability for the audio-visual integration, we measured EEG from 37 participants (10 females) during a McGurk task (Oozono & Mizuhara, in prep.). By changing presentation intervals between visual and auditory stimuli, we tested whether the phase shift of neural oscillation appeared in association with visual/auditory input. The frequencies of neural oscillation corresponded well with the behavioral results of the McGurk effect, confirming that the audio-visual information was integrated at an ideal phase of neural oscillation. Taken together, the phase shift and amplitude suppression caused by anticipatory input would result in enhancing neural excitability when following visual/auditory input. Our results demonstrated that there are two different mechanisms of phase coding involved in the integration of multimodal information: phase shift and amplitude suppression of slow neural oscillation.

Disclosures: H. Mizuhara: None. **T. Kumagai:** None. **A. Oozono:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 689.01/II8

Topic: E.03. Basal Ganglia

Title: Differential contribution of striatal pathways activity to action selection after reward and aversive learning

Authors: *M. LANGE, H. KAKINUMA, B.-W. CHERNG, T. SHIRAKI, T. ISLAM, H. HAMA, A. MIYAWAKI, H. OKAMOTO
Brain Sci. Inst., RIKEN, Wako-Shi, Saitama, Japan

Abstract: Action selection among several choices to adapt animal behavior is a fundamental cognitive process, well conserved in animal kingdom. It is well documented that neuronal circuits of the corticobasal ganglia are critical for decision-making in mammalian. Particularly, it has been classically hypothesized that two basal ganglia pathways mediate generation of action via opposing role: the direct pathway by *approach* (Go behavior) and the indirect by *avoidance* (NoGo behavior). We have elucidated that zebrafish *Danio rerio*, has partially the equivalent structure as the mammalian corticobasal ganglia circuitry, and that zebrafish telencephalon contains the direct- and indirect-like neuronal populations essential in action selection during reward and aversion reinforcement.
By combining transgenic animal, Rabies-virus tracing system and Scale tissue clearing technology we generate brain wide maps of neurons sending projection to the striatal direct or indirect pathway. We discovered that the majority of the inputs of the striatal pathway arise from the zebrafish dorsal pallial neurons (functionally equivalent to the mammalian cortex). Overall, our results determine that the corticobasal ganglia circuitry is conserved throughout vertebrates - from Zebrafish to Primates.
Then, using the genetically encoded calcium indicator GCaMP7, we recorded the brain activity in the striatal pathway in trained zebrafish for either positive (i.e. food) or aversive (i.e. electric shock) reinforcement learning, during behavioral cue presentation. Using a cranial window implementation and two-photon imaging we record at single cell resolution the striatal pathways activities. We observed that the striatal activity, mediating Go or NoGo behavior, is dependent of the conditioning reinforcers (negative or positive) after learning. Our results reconsider the classical view of corticobasal ganglia function mediating opposite effects, and support a cooperative model depending on the behavioral valence of the situation.

Disclosures: **M. Lange:** None. **H. Kakinuma:** None. **B. Cherng:** None. **T. Shiraki:** None. **T. Islam:** None. **H. Hama:** None. **A. Miyawaki:** None. **H. Okamoto:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

Location: Halls A-C

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Program#/Poster#: 689.02/II9

Topic: E.03. Basal Ganglia

Support: NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

Title: Direct functional innervation of dorsolateral striatum spiny projection neurons by the amygdala

Authors: C. CUNHA, R. SUDDLE, C. GAZZOLA, A. VIJENDRAN, *J. L. PLOTKIN
Neurobio. and Behavior, Stony Brook Univ. Dept. of Neurol., Stony Brook, NY

Abstract: The striatum is loosely organized in a somatotopic fashion, with striatal subregions preferentially receiving similar types of excitatory inputs. For example, the dorsolateral striatum is robustly innervated by the somatosensory cortex and thalamus, whereas the ventral striatum receives inputs from more limbic-associated brain regions. Recent anatomical work has highlighted that while striatal spiny projection neurons (SPNs) in the dorsal striatum predominantly receive sensory and motor related inputs, a small number of limbic-related inputs also converge on the same SPNs (Wall et al., 2013). While such convergence would suggest a potential mechanism by which dorsal striatum-mediated action selection and habit learning can be directly influenced by limbic-associated cues, direct functional evidence of such synaptic connections is scant. Here we use a combination of electrophysiology, 2-photon calcium imaging and optogenetics to demonstrate that both direct and indirect pathway SPNs in the dorsolateral striatum are functionally innervated by the basal and lateral nuclei of the amygdala (BLA). Channelrhodopsin 2 (ChR2) was stereotaxically expressed in the BLA of drd2-eGFP and drd1-tdTomato transgenic mice, SPNs voltage clamped in acute brain slices and synaptic contacts visualized by marching a blue laser (approximately 10 micrometers in diameter) along the dendrite and measuring the location of NMDA receptor-mediated calcium transients. Using this technique we observed that functional BLA inputs are a) disperse, with typically no more than 5 contacts per 100 micrometer stretch of dendrite, b) distributed similarly across proximal and distal dendrites and c) preferentially target dendritic shafts as opposed to spines. Synchronized activation of BLA inputs with the blue laser targeted to a distal dendrite in current clamp mode was capable of evoking somatic action potentials. Action potentials were followed by a prolonged depolarization lasting tens of milliseconds, similar to that evoked by optogenetic activation of cortical terminals, but significantly scaled down in both amplitude and duration. The implications of BLA synaptic inputs on corticostriatal synaptic integration are currently being investigated.

Disclosures: C. Cunha: None. **R. Suddle:** None. **C. Gazzola:** None. **A. Vijendran:** None. **J.L. Plotkin:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

Location: Halls A-C

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Program#/Poster#: 689.03/II10

Topic: E.03. Basal Ganglia

Support: NIH Grant MH0800055

UF CTSI KL2 TR000065

Title: Pharmacological targeting of the striatal indirect basal ganglia pathway neurons improves subthalamic nucleus dysfunction and treats repetitive and compulsive behaviors in mice

Authors: *A. M. MUEHLMANN[1], K. BOSWELL[2], M. A. KING[3], M. H. LEWIS[4]
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Abstract: Repetitive, restricted, and compulsive behaviors are common phenotypic traits of neurodevelopmental, neurological, and psychiatric disorders. Although antidepressant medications have been used with some success in individuals with obsessive compulsive disorder (OCD), they're not effective for all OCD patients and have not been FDA approved for treatment of repetitive behaviors in other disorders. Based on our findings of lower indirect basal ganglia pathway function in mouse models of repetitive behavior, we have designed a drug cocktail that targets the relevant cell type in striatum to boost pathway function. This drug cocktail is made up of a dopamine D2 receptor antagonist, an adenosine A2A receptor agonist, and a glutamate mGluR5 positive allosteric modulator. We found this drug cocktail significantly reduces repetitive behavior in two mouse models (deer mice and C58 mice) and dramatically lessens the incidence of excessive grooming-induced tissue trauma in an OCD mouse model (*Sapap3* knockout mouse). These improvements in behavior are associated with altered gene expression profiles and increased dendritic spine density in the subthalamic nucleus, an important driver of indirect basal ganglia pathway output. These data suggest that repetitive and compulsive behaviors share neuropathological features and that a drug cocktail that targets dopamine, adenosine, and glutamate receptor heteromeric complexes may offer pharmacotherapeutic benefit to many neurodevelopmental, neurological, and psychiatric disorders.

Disclosures: A.M. Muehlmann: None. **K. Boswell:** None. **M.A. King:** None. **M.H. Lewis:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 689.04/II11

Topic: E.03. Basal Ganglia

Support: HHMI visiting scientist program

Title: Distinct roles of substantia nigra projection neurons in controlling orienting movements

Authors: *E. A. STUBBLEFIELD[1], G. FELSEN[2], J. T. DUDMAN[1]
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Abstract: Purposive behavior requires making appropriate responses to salient stimuli. The appropriate response to a stimulus involves accurate execution of the response (sensorimotor mapping) and inferring, from prior experience, stimuli that are informative about future outcomes (rewards). The superior colliculus (SC) is a critical node in controlling orienting responses to salient stimuli. The inhibitory projection from the output nucleus of the basal ganglia, substantia nigra pars reticulata (SNr), to the deep layers of the SC (SNr^{SC} neurons) is thought to be a permissive gate that determines when orienting movements will be driven by SC output. SNr activity reflects features of reinforced behaviors including reward expectations, and thus the SNr^{SC} projection may allow reinforcement history to influence the control of orienting movements. However, the specificity of information conveyed by the SNr^{SC} projection relative to the population activity of SNr remains poorly described. In addition, it is unclear whether SNr^{SC} neurons modulate orienting responses selectively when reward history is informative.
We developed a novel head-fixed orienting task to tease apart the potentially distinct roles of SNr^{SC} and $SNr^{non\text{-}SC}$ neurons mediating visual discrimination, reinforcement-based decisions, and motor output. Mice are trained to rotate a wheel left or right with their forelimbs to bring an eccentric visual stimulus to the center of their visual field to obtain reward. We use two versions of this task: 1. A blocked trial structure in which trial-side is determined by a Markov process with a fixed transition rate, and 2. A randomized trial-side structure. In blocked trials, reward history is informative of current choice, and average performance quickly reaches 89% correct. In randomized trials, reward history is not informative, and mice require more training to perform better than chance, ultimately reaching an average performance of 77%
In behaving transgenic mice expressing ChR2 in SNr neurons, SNr^{SC} neurons were antidromically isolated via optical "tagging," allowing us to compare task-related activity between SNr^{SC} neurons (tagged) and putative $SNr^{non\text{-}SC}$ neurons (untagged). Both neuron types exhibit activity changes related to stimulus presentation, movement, and reward. This cell-type specific recording approach will allow us to assess whether and how the contribution of SNr^{SC} neurons, as well as putative $SNr^{non\text{-}SC}$ neurons, differs when reward history is and is not predictive of the rewarded movement.

Disclosures: E.A. Stubblefield: None. **G. Felsen:** None. **J.T. Dudman:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

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Topic: E.03. Basal Ganglia

Support: CAPES

CNPq

FAPESP

Title: Effects of globus pallidus or substantia nigra pars reticulata inactivation in startle reflex and locomotor behavior

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Abstract: The capability to stop an action in course is important for living animals and might occur for many reasons in a way to reach a goal or survive. Basal ganglia (BG) are considered to be the one of the main neural substrate, at least in mammals, that allows initiate and stop a behavior. Consistently, BG dysfunction terminates in loss of behavioral arrest. Prepulse Inhibition (PPI) is an example of this type of behavioral modulation. During PPI, the animals have to inhibit the startle response to a suddenly sensorial stimulus. Accordingly, patients with BG deficits (e.g. Schizophrenia, Parkinson, TOC) also share low indices of PPI. Classically, BG contains two dopaminergic-mediated pathways that are distinguished by function. The direct pathway is excitatory and promotes the movement. The indirect pathway otherwise, is inhibitory and block the motor programs. Therefore, the objective of this study was to verify the contribution of direct and indirect pathways on PPI and locomotion by inhibiting their target regions. Muscimol infusions into the entopeduncular nucleus (named in primates, globus pallidus internal segment, GPi) or substantia nigra reticulata (SNr) - direct pathway targets - induced PPI deficit by increasing startle, despite a decreasing in animals exploratory behavior. Conversely, indirect pathway inhibition - after muscimol infusion into globus pallidus (external segment, GPe) - has no effect on PPI and startle, but tends to increase the locomotor activity in open field test. Recently, studies using optogenetics techniques showed that the control of these two dopaminergic pathways over behavior can be more complex than previously believed: both pathways can be active during an ongoing action. Together, these results can contribute to elucidate the role of BG in inhibitory outcomes and to develop more effective therapeutics to treat BG related diseases.

Disclosures: S. Rodrigues: None. **T.L. Ferreira:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

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Topic: E.03. Basal Ganglia

Support: DFG EXC294

DFG EXC307

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Title: The descending diencephalic dopamine system is tuned to sensory stimuli

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Abstract: The vertebrate diencephalospinal dopaminergic system (A11 in mammals) provides the sole dopaminergic innervation of hindbrain and spinal cord, and has been implicated in modulation of locomotion and sensory processes. However, exact contributions of sensory stimuli and motor behavior to A11 dopaminergic activity remain unclear. We recorded cellular calcium activity in four anatomically distinct posterior tubercular A11-type dopaminergic subgroups, and in two adjacent hypothalamic dopaminergic groups, using *th:Gal4* and *UAS:GCaMP7a*-transgenic, semi-restrained zebrafish larvae. Correlation of calcium activity to motor behavior and specific sensory stimuli revealed the contributions of different sensory modalities and motor states to dopaminergic activity. Each posterior tubercular and hypothalamic subgroup showed distinct activity patterns, while activity was synchronous within individual subgroups. Caudal and dorsomedial hypothalamic dopaminergic neurons are activated following vigorous tail movements, and stay active for about 10 seconds, revealing predominantly post-motor activity. In contrast, posterior tubercular dopaminergic neurons are predominantly sensory driven, with subgroups differentially responding to different tactile or visual sensory modalities. In the most rostral posterior tubercular dopaminergic subgroup, neuronal response magnitudes are tuned to tactile stimulus intensities, revealing features similar to sensory systems. We identify the lateral line system as source for this tactile tuning. In contrast, caudal posterior tubercular dopaminergic neurons are responsive to distinct moving visual stimuli. Specifically, translational forward stimuli, which may indicate insufficient rheotaxis and drift, induce dopaminergic activity, but backward or rotational stimuli not. The activation of posterior tubercular dopaminergic neurons by sensory stimuli, and their projections onto peripheral mechanosensory systems, suggest a participation of A11-type neurons in the feedback regulation of sensory systems. Together with the adjacent hypothalamic neurons they may serve to set basic behavioral states.

Disclosures: **W. Driever:** None. **S. Reinig:** None. **A. Arrenberg:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

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NSERC 386396

Fonds de recherche du Québec - Santé (FRQS)

La société Parkinson du Québec

Title: The hyperdirect pathway in cynomolgus monkeys: A single-axon tracing study

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Abstract: This study provides the first detailed description of individual axons that form the hyperdirect pathway in monkeys. These axons, which arise from the motor cortex and provide a major glutamate-mediated excitatory input to the subthalamic nucleus (STN), were studied individually in cynomolgus monkeys (*Macaca fascicularis*) following microiontophoretic injections of biotinylated dextran amine in layer V of the forelimb area of the primary motor cortex (M1). Singly-labeled axons were reconstructed in 3D from serial sections using a computerized image analysis system. The innervation of the STN arising from M1 derives essentially from collaterals of long-ranged corticofugal axons en route to the brainstem. Typically, after leaving M1, these large caliber axons (1.7-3.7 µm) enter the internal capsule and travel between the caudate nucleus and putamen without providing any collaterals to the striatum. More ventrally, they emit a thin collateral (0.2-1.6 µm) that runs lateromedially within the dorsal region of the STN, providing boutons en passant in the sensorimotor functional territory of the nucleus. Occasionally, the lateromedially coursing collateral breaks out into thinner and varicose branches that plunge ventrally into the STN. In some cases, its medial tip invades the lenticular fasciculus dorsally and yields a few beaded axonal branches in the zona incerta, whereas in other cases, the collateral runs caudally and innervates the ventrolateral region of the red nucleus in which large axon varicosities are observed, many displaying a perisomatic arrangement. One axon was seen to yield thin collaterals that departed form the internal capsule to arborize in the reticular thalamic nucleus before reaching the STN. Only one neuron had an axon that reached the STN without continuing its route to the brainstem. It remains thin as it travels in the internal capsule, exhibiting small-sized axon varicosities in this

major fiber bundle as well as in the zona incerta. Altogether, our findings indicate that the so-called hyperdirect pathway is in fact largely indirect, as it derives essentially from collaterals of long-ranged corticofugal axons en route to the brainstem. Furthermore, these collaterals are not solely devoted to the STN, as they also innervate the red nucleus and/or the zona incerta. Such detailed knowledge of the primate hyperdirect pathway is essential to reach a better understanding of the anatomical and functional organization of the primate basal ganglia. It is likely to help unraveling the poorly known mechanisms that underlie the therapeutic effect of deep brain stimulation (DBS) often used to alleviate motor symptoms of Parkinson's disease.

Disclosures: D. Coudé: None. **A. Parent:** None. **M. Parent:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

Location: Halls A-C

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Program#/Poster#: 689.08/II15

Topic: E.03. Basal Ganglia

Title: One critic, two actors

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Abstract: We propose a new hypothesis concerning the dissociated role of the basal ganglia in the selection and the evaluation of action that has been formulated using a theoretical model and confirmed experimentally in monkeys. To do so, prior to learning, we inactivated the internal part of the Globus Pallidus (GPi, the main output structure of the BG) with injections of muscimol and we tested monkeys on a variant of a two-armed bandit task where two stimuli are associated with two distinct reward probabilities (0.25 and 0.75 respectively). Unsurprisingly, performance in such condition are at the chance level because the output of basal ganglia is suppressed and they cannot influence behaviour. However, the theoretical model predicts that in the meantime, values of the stimuli are nonetheless covertly evaluated and learned. This has been tested and confirmed on the next day, when muscimol has been replaced by a saline solution: monkeys instantly showed significantly improved performances (above chance level), hence demonstrating they have covertly learned the relative value of the two stimuli. This tends to suggest a competition takes place in the Cortex-BG loop between two actors, one of whom being sensitive to criticism and the other not. Ultimately, the actual choice is valuated, independently of the origin of the decision.

Disclosures: T. Boraud: None. **D. Kase:** None. **M. Topalidou:** None. **N. Rougier:** None.

Poster

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Topic: E.03. Basal Ganglia

Support: Howard Hughes Medical Institute

Title: Integrated basal ganglia pathway activity controls execution during reaching and freely moving behavior

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Abstract: The prevailing theory of action selection suggests that the opposing pathways of the basal ganglia (BG), an evolutionarily conserved subcortical area, promote or suppress action, respectively. However, diseases afflicting the BG - such as Parkinson's disease - are characterized by an impairment of *how* actions are executed rather than an inability to select the actions themselves. We found that biasing BG activity does not promote or suppress movement, but instead, bidirectionally selects and reinforces execution parameters in a dopamine-dependent manner (Yttri and Dudman, *Nature* 2016).
Our current work further distinguished between putative BG functions of action gating and performance control. We employed brief optogenetic stimulation to either the direct or indirect pathway whenever a freely moving animal paused locomotion. Gating models predict that direct pathway stimulation should induce locomotion, while indirect pathway stimulation should prolong stopping. However, our selective stimulation produced the opposite: direct pathway activation prolongs pausing while indirect pathway stimulation shortens pausing. The converse held true when selective stimulation was applied during locomotion.These data are consistent with our stimulation in closed-loop with reach velocity but stand in sharp contrast to previous studies using prolonged, indiscriminate stimulation. We then proceeded to explore the range of execution parameters for which closed-loop stimulation can sculpt performance and how biasing BG activity interacts in the context of dopamine release and Parkinson's disease.
Finally, we investigated how the striatum might accomplish this execution control, and particularly how striatal neuronal ensembles function as dynamical systems. We discovered that the striatum encodes not only the start and stop of a reach, but also other control parameters such as velocity, amplitude and duration – a profoundly greater level of detail than previously thought. Then, utilizing a simple decoder, we were able to predict the full path and velocity of a individual reaching movement over 140 milliseconds before it is performed, positioning the BG to actively drive changes in the kinematics of movements. This fundamental shift in the

paradigm of BG function has important implications for our understanding of action selection and human disease that will be pursued in the newly started Yttri Lab.

Disclosures: E.A. Yttri: None. **B. Panigrahi:** None. **J.T. Dudman:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

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Topic: E.03. Basal Ganglia

Support: Lundbeck Foundation R194-2015-727 (MR)

Danish Parkinson Association (MR)

Weiman Fellowship (MR)

Title: Chemogenetic inhibition of direct-pathway neurons in dorsomedial striatum reduces locomotor activity in mice supporting the role of the direct pathway in promoting movement

Authors: *M. RICKHAG, C. CIRIACHI, A. BAY-KØNIG, U. GETHER
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Abstract: The striatum is the main input structure of the basal ganglia, a series of subcortical nuclei that play a key role in motor control. Two distinct basal ganglia circuits, the direct and the indirect pathways, originate from the striatal projection neurons and are canonically believed to respectively facilitate and oppose motor behavior. Ablation studies have revealed that distinct striatal compartments have different functions in the regulation of movement, yet their role is still unclear. In order to get a deeper understanding of striatal compartmentalization and to validate the contextual function of the basal ganglia circuits, we aimed at selectively modulate the activity of direct pathway-medium spiny neurons (dMSNs) in the dorsomedial striatum (DMS). This specificity was achieved by viral-genetic tools combining the Cre-driver mouse lines (D1R-Cre) and chemogenetic tools, the *Designer Receptors Exclusively Activated by Designer Drugs* (DREADDs). This approach allowed us to remotely control signal transduction in selective neurons and, therefore, to modulate specific neuronal pathways in a limited time window. Here, we show that activation of inhibitory (Gαi-associated) DREADD in DMS-dMSNs significantly decreased locomotor activity in the open field test. DREADD-mediated inhibition was also able to reduce locomotor activity following acute cocaine administration. To validate the involvement of Gi- protein signaling pathway upon DREADDs activation, we analyzed downstream effectors via immunohistochemistry and immunoblotting techniques. Moreover, we confirmed that DREADDs expression in the striatum was restricted to the dorsomedial region and showed both somatic and axonal/dendritic localization. Overall, our

results provide further evidence supporting the role of the direct-pathway in promoting movement.

Disclosures: **M. Rickhag:** None. **C. Ciriachi:** None. **A. Bay-Kønig:** None. **U. Gether:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

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Carl Zeiss Stiftung

Title: Effect of correlations and sensory responses in the basal ganglia on the transmission of motor signals to the thalamus

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Abstract: One prominent feature of Parkinson's disease is the emergence of correlated activity in basal ganglia output neurons. In contrast, in healthy animals, the activity in basal ganglia output regions is usually uncorrelated, potentially due to active decorrelation (Wilson, 2013). However, the functional role of active decorrelation on the transmission of motor signals from the basal ganglia to the downstream regions including ventral thalamus is unknown. Basal ganglia output neurons (e.g. in the substantia nigra pars reticulata; SNr) may transmit motor signals by decreasing their firing rate during movement initiation. Such decreases in SNr firing rate can lead to post-inhibitory rebound spikes in downstream thalamic neurons (Goldberg et al., 2013).
To study potential functional roles of active decorrelation, we investigated the effect of correlations among SNr neurons on rebound spikes in a Hodgkin-Huxley model of a thalamocortical neuron (Rubin et al., 2004). We found that uncorrelated SNr inputs lead to rebound spikes briefly after the movement-related decrease in firing rate. In addition, despite

stochastic inputs, the latency from the decrease to the onset of the rebound spike showed small trial-to-trial variability. In contrast, correlated SNr inputs lead to rebound spikes not only after the movement-related decrease, but also at random times. This is because the correlated input spike trains are more likely to contain brief pauses without spikes, which trigger a "random" rebound spike. Furthermore, the latency of the movement-related rebound spikes became variable over trials.
In addition to movement-related decreases, SNr neurons briefly increase their firing rate in response to sensory stimuli such as "Go" and "Stop" cues in a stop-signal task (Schmidt et al., 2013). We studied the effect of such sensory responses in SNr on the transmission of motor signals. We found that sensory responses up to 30 milliseconds before the movement-related decrease facilitated the generation of movement-related rebound spikes. In contrast, SNr firing rate increases after the onset of the movement-related decrease suppressed rebound spikes. Therefore, the timing of the sensory responses determined whether they promoted or suppressed movement, indicating an important functional contribution in sensorimotor integration.
In conclusion, active decorrelation in basal ganglia output may promote the transmission of motor signals via rebound spikes. Pathological correlations impair this transmission by increasing the trial-to-trial variability and the number of movement-unrelated rebound spikes, which may be related to motor symptoms in Parkinson's disease.

Disclosures: M. Mohagheghi Nejad: None. **S. Rotter:** None. **R. Schmidt:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

Location: Halls A-C

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Topic: E.03. Basal Ganglia

Title: Electrophysiology of rat motor thalamus reveals unique patterns of firing during movement

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Abstract: The thalamus is commonly regarded as a relay nucleus, but it is increasingly appreciated that it is a critical node in shaping normal and pathological motor behaviors. It remains unclear how its primary inputs from the basal ganglia, cerebellum, and cortex differentially contribute to the cortical-bound output of the "motor thalamus". To determine behavioral correlates of neuronal activity in the rat motor thalamus we performed electrophysiology during a cued choice reaction time task. We found task-specific firing rate modulations for all behavioral events based on single unit neuronal classifications. This included neurons that rapidly increased their firing rate in response to sensory cues, neurons that showed

tonically sustained firing during all movements, and neurons that showed rhythmic increases in firing rate precisely at movement onset. We performed a detailed investigation of neuronal activity specifically associated with the movement onset population as it has specific implications to movement disorders characterized by the inability to initiate movements (e.g. Parkinson's disease). These neurons' firing rates are depressed during a hold period prior to cued movement initiation. This is consistent with standard thalamocortical firing rate models which suggest GABAergic afferents from the basal ganglia regulate movement through disinhibition. Secondly, the burst frequency across these neurons was highly regular and consistently in the theta band (4-8 Hz). Finally, many of these neurons fired more strongly for contralateral movements. Ongoing work is directed at determining whether these functional classifications are correlated with distinct anatomic or physiologic features (e.g., cerebellar vs basal ganglia afferents), and how these activity patterns are generated.

Disclosures: M. Gaidica: None. **C. Cyr:** None. **A. Hurst:** None. **A. Kamath:** None. **D.K. Leventhal:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

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Topic: E.03. Basal Ganglia

Support: DA019473

DA038412

Title: Movement-related encoding in the ventral pallidum

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Abstract: The ventral pallidum (VP) is the main output nucleus of the nucleus accumbens (NAc) and essential for translating limbic sensory, value and motivation signals into motor output, but how it does so is unknown. To assess what role the VP plays in motivated behaviors, particularly in regards to locomotion, we recorded from the VP of food-restricted rats performing a discriminative stimulus (DS) task. The DS was an auditory cue, presented at variable intervals, which directed the rat to approach and press a lever to obtain 10% sucrose reward. A lever press during the 10 s DS resulted in reward delivery and cue termination. Trained animals were implanted with microelectrode arrays in the VP. Video tracking of head-mounted LEDs enabled detection and measurement of locomotion. Our results show that approximately half of the

neurons in the VP were excited by DS presentation, while a small proportion (~15%) were inhibited. Moreover, after DS presentation, neural firing rates were positively correlated with movement initiation latency. In a largely different population of VP neurons, changes in activity were highly correlated with initiation and cessation of spontaneous locomotor movements (i.e., movements during the inter-trial interval that were typically not directed towards the lever). Typically, neurons that showed inhibition during movement onset were excited during movement cessation, and vice versa. These results suggest that the ventral pallidum is involved in, and may be necessary for, initiation and cessation of movement, and the translation of emotionally salient sensory stimuli into motor action.

Disclosures: **J.D. Lederman:** None. **S. Lardeux:** None. **S.M. Nicola:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

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Topic: E.03. Basal Ganglia

Support: BrainLinks-BrainTools, Cluster of Excellence funded by the German Research Foundation (DFG, grant number EXC 1086)

Title: Different population coding schemes in basal ganglia subregions during movement

Authors: *A. JIMENEZ RODRIGUEZ[1], N. M. MALLET[3], D. K. LEVENTHAL[4], J. D. BERKE[5], R. SCHMIDT[2]
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Abstract: Basal ganglia circuits are involved in motor control, including the initiation and cancellation of movements. While movement-related firing rate changes of single neurons have been described in different basal ganglia subregions and cell types, the underlying population code remains unclear. Here we apply advanced data analysis techniques to a large data set of electrophysiological recordings in rats performing a stop-signal task to study such coding schemes.
Firstly, we describe the population coding schemes in terms of their sparseness and heterogeneity. Here we consider sparseness as the fraction of neurons changing their firing rate during an event (e.g. movement initiation). We derived a novel sparseness measure from the components of the eigenvectors of the covariance matrix taken as the neuron's contribution to overlapping patterns. This measure is more informative, compared to other measures, when

different patterns of activation are multiplexed in the population. Heterogeneity describes the diversity in the firing patterns. Using coding theory we define heterogeneity as the average "codeword length" of a particular prefix code computed from the population and relate it to minimum redundancy codes represented by Huffman trees. We provide an algorithm for constructing one of such trees. We find that the coding scheme in the population of striatal medium spiny neurons is sparse and heterogeneous. In contrast, the code in the substantia nigra pars reticulata is distributed and homogeneous. This points to the input and output stages of the basal ganglia having opposite coding strategies.
Secondly, we use dimensionality reduction techniques to generate low-dimensional trajectories that characterize diverse firing patterns during movement initiation. To do so, we provide means of mapping population parameters to the geometry of the trajectory. We also suggest ways of comparing trajectories (e.g. from long and short reaction times) and studying the effect of preprocessing steps (e.g. smoothing the firing rate) in distorting the trajectory shape. We find that basal ganglia subregions and cell types have distinct population trajectory shapes. In particular the output region of the basal ganglia (substantia nigra pars reticulata) shows an almost linear evolution around movement initiation. In contrast, other basal ganglia subregions show more curved trajectories during movement initiation.
Our results indicate that different basal ganglia subregions employ different population coding schemes during movement and this might reflect different functional contributions to the processing of motor signals.

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Poster

689. Subcortical Physiology and Regulation of Behavior

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Topic: E.03. Basal Ganglia

Support: CHDI Foundation

Title: Homeostatic motor adaptation: Cerebellum's failure emboldens basal ganglia

Authors: *R. A. CAPPS, D. TODOROV, W. BARNETT, Y. MOLKOV
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Abstract: The cerebellum and basal ganglia (BG) are both vital for motor adaptation. The cerebellum is believed to be responsible for error-based (supervised) learning, comparing visual input with an internal representation of the environment. The BG are thought to be responsible for non-error based (reinforcement) learning. Although their roles have been investigated

independently, the interplay between BG and cerebellum remains unclear. Some studies suggest that when visual input is unreliable, the cerebellum stops influencing movements. To investigate this phenomenon, we designed a network model with the cerebellum implemented as a phenomenological node, and the BG implemented as a firing-rate model. Our model describes a homeostatic mechanism by which motor control shifts from the cerebellum to the BG when a perception perturbation is too strong for the error-based learning mechanism to be effective. We used the model to simulate behavioral experiments by Gutierrez-Garralda et al. (2013) in which subjects throw a ball at a target with their vision perturbed by a prism reflecting about a vertical axis. Such a visual perturbation causes error-based motor adaptation to correct the movement in the opposite direction thus having an adverse effect on the performance. This occurs because cerebellar correction relies on vector error, which if reflected, also reflects the correction. To avoid mal-adaptation, we suggest that cerebellum contains an adaptive critic mechanism, which compares the current error to a previously observed error. If the error decreases predictably, the adaptive critic facilitates cerebellum to further correct the movement. Otherwise, the adaptive critic suppresses cerebellar learning. In the above experiments the subjects could still improve throwing accuracy in a non-error-based manner, supposedly by reinforcement learning mechanisms. The non-error-based correction in the model is provided by BG via reinforcement learning. The reward for each movement depends on proximity to the target. The BG learn to reinforce/block actions based on reward-prediction error (RPE), which is calculated as the difference between the expected/previous reward and current reward values. If visual perturbation does not alter the subject's perception of the vector error, the cerebellum mediated adaptation leads to gradual improvement in movement accuracy, thus generating a positive RPE, which reinforces the action chosen by BG. Thus in these conditions, motor adaptation is exclusively guided by cerebellum. In contrast, perturbations that lead to cerebellar mal-adaptation result in a negative RPE stimulating the BG to search for more rewarding actions.

Disclosures: **R.A. Capps:** None. **D. Todorov:** None. **W. Barnett:** None. **Y. Molkov:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 689.16/II23

Topic: E.03. Basal Ganglia

Support: NIH DA025303

Navicent Health Research Award

Title: Patch compartment lesions reduce habitual sucrose consumption

Authors: *K. A. HORNER, J. B. LOGUE, T. A. JENRETTE
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Abstract: The striatum mediates habit formation and reward association. The striatum can be divided into the patch and matrix compartment, which are two neurochemically and anatomically distinct regions that may sub-serve different aspects of behavior. For example, the patch compartment may mediate reward-related behaviors, while the matrix compartment may mediate adaptive motor functions. Furthermore, previous studies have shown that enhanced relative activation of the patch versus matrix compartment is associated with inflexible behaviors, such as stereotypy. Habitual behaviors are also inflexible in nature, but whether enhanced activation of the patch compartment contributes to habitual behavior is not known. The goal of the current study was to examine the role of patch compartment neurons in the development of habit formation. We used dermorphin-saporin to specifically ablate neurons of the patch compartment prior to training animals to self-administer sucrose on a random interval schedule of reinforcement, which has been shown to foster habit formation. Our data showed that destruction of the neurons of the patch compartment prevented the reinstatement of sucrose self-administration after sucrose devaluation, indicating that absence of the patch compartment interrupted the development of habitual behavior. Our data also indicate that c-Fos levels were decreased in the dorsolateral striatum (DLS) and sensorimotor cortex (SMC), but increased in dorsomedial striatum (DMS) and prefrontal cortex (PFC) in patch-lesioned animals that did not develop habitual behavior, indicating that diminished habit formation is associated with decreased activation of regions that participate in habitual behavior, and increased in regions associated with goal-directed behaviors. Together, these data indicate that the patch compartment participates in habit formation by altering the flow of information through basal ganglia circuits.

Disclosures: K.A. Horner: None. **J.B. Logue:** None. **T.A. Jenrette:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 689.17/II24

Topic: E.03. Basal Ganglia

Title: Anatomical and functional characterization of parvalbumin-expressing neurons in the mouse external globus pallidus

Authors: *V. LILASCHAROEN[1], E. H. WANG[2], A. N. TRAN[1], X.-Y. WANG[1], B. LIM[1]
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Abstract: The external globus pallidus (GPe) is one of the major nuclei of the basal ganglia, a group of subcortical nuclei that are critically involved in voluntary movements and is therefore

strongly implicated in movement disorders such as Parkinson's disease. According to the classical model of basal ganglia circuitry, the GPe is considered to be a homogeneous structure that functions as a relay station in the indirect pathway receiving afferents from the striatum and sending GABAergic efferent to the subthalamic nucleus (STN). However, classifying the GPe circuit organization is complicated by the fact that a single GPe neuron can send axonal collaterals to multiple brain structures, suggesting a more complex model of circuit architecture and information processing in the basal ganglia. By using a novel viral-genetic approach, we have identified two distinct populations of parvalbumin-expressing neurons in the GPe (GPe-PV) based on their projections to either the parafascicular thalamic nucleus (PF) or the substantia nigra pars reticulata (SNr). We will further apply a combination of electrophysiological, viral-genetic approaches, and *in vivo* imaging to provide a comprehensive framework on anatomical and functional organization of the GPe-PV neurons and to demonstrate how different GPe-PV populations undergo changes in animal models of Parkinson's disease.

Disclosures: V. Lilascharoen: None. **E.H. Wang:** None. **A.N. Tran:** None. **X. Wang:** None. **B. Lim:** None.

Poster

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Topic: E.03. Basal Ganglia

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CIHR grant 81321

Neuroscience Research group (GRSNC) of the University of Montreal

Title: Tardive dyskinesia induced by prolonged antipsychotic treatment in monkeys is associated with Akt pathway activity in dopamine D3 receptor expressing cells of the putamen

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Abstract: The pathophysiology of tardive dyskinesia (TD) remains elusive. This delayed and potentially irreversible motor complication arises after chronic exposure to centrally acting dopamine $D_{2/3}$ receptor antagonists such as antipsychotic drugs. Antipsychotics modulate

multiple kinase pathways, but their involvement in TD is not well understood. To investigate the neurochemical basis of TD, we exposed capuchin monkeys to prolonged haloperidol (N = 11) or clozapine (N = 6) treatments. Six untreated animals were used as controls. Five haloperidol-treated animals developed TD similar to that found in humans. No TD was observed in the clozapine group. Using Western blots, we measured total and phosphorylated protein kinase levels (normalized over GAPDH or tubulin protein levels) previously associated with dopamine $D_{2/3}$ receptor signaling cascades in the putamen. While haloperidol enhanced phospho[Thr202/Tyr204]-p44/42 (pERK1/2) levels by 3.4 fold, no difference was observed between dyskinetic and non-dyskinetic monkeys. On the other hand, phospho[Th34]-DARPP-32 levels were induced by 1.7 fold only in dyskinetic animals. Interestingly, haloperidol specifically reduced putamen GRK6 (64%), β-arrestin2 (57%) and phospho[Ser9]-GSK-3β (pGSK-3β) (69%) levels in haloperidol-treated animals which developed TD, whereas phospho[Ser473]-Akt (pAkt) levels were upregulated in this subgroup (183%), and positively correlated ($r^2 = 0.590$, p value = 0.0022) with TD scores. Levels of phosphorylated protein kinases observed in the clozapine group were generally similar to controls and non dyskinetic animals treated with haloperidol. But, GRK6 protein levels were upregulated 1.7 fold by clozapine. Total protein kinase levels were not altered by any treatment. Previous results in our laboratory correlated an upregulation of striatal D_3 (not D_2) receptors with TD. Using double immunohistochemistry, we observed an increase of pAkt/D_3 colocalization (140%) in the putamen of dyskinetic monkeys, as compared to non TD animals. Our results suggest that upregulation of D_3 receptors and alterations in the GRK6/β-arrestin2/Akt/GSK-3β molecular cascade are associated with the development of TD in this non human primate model.

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Poster

689. Subcortical Physiology and Regulation of Behavior

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Topic: E.03. Basal Ganglia

Title: Event-related stimulation of subthalamic nucleus alters conflict-related control in a time period overlapping with low-frequency activities

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Abstract: The subthalamic nucleus (STN) of the basal ganglia is implicated in controlling responses during conflict. Several human deep brain recording studies have shown that conflicting responses are related to increased STN power in low frequencies (delta-theta, 2-8Hz). Yet, whether the STN and/or its associated circuitry is critical in implementing conflict-related control, and the temporal dynamics of this putative critical effect are unknown. Using a novel event-related deep brain stimulation paradigm, we transiently disrupted the STN and/or its related circuits during a Stroop task. The subjects were required to name the font color and ignore the word meaning, yielding non-conflict (word meaning and color matched) and conflict (no match, word-meaning caused a bias) conditions. In a double-blinded design, we delivered short bursts of stimulation at three time points: at the beginning of trial when a cue signaled subject to get ready; and early close to word cues and late close to responses. Stimulation had no significant effect on RT of non-conflict trials, but on conflict trials, it made subjects respond relatively faster ($F(3,30)=3.379$, $P=0.03$). Further, stimulation generally made subjects *less* accurate when applied selectively early in the response period ($P=0.01$). This time period corresponded with increased low frequency power for the contrast of conflict and non-conflict. These results provide causal evidence in humans that the STN and/or its associated circuitry is critical for processing response conflict, and that the period of LFO power increase is associated with suppressing errors. Our results provide temporal information about the dynamics of when such control occurs.

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Poster

689. Subcortical Physiology and Regulation of Behavior

Location: Halls A-C

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Program#/Poster#: 689.20/II27

Topic: E.03. Basal Ganglia

Title: Glutathione depletion in the SNpc modifies the nigrostriatal plasticity in rats

Authors: *M.-L. DÍAZ HUNG[1], E. ALBERTI[2], L. BLANCO LEZCANO[3], N. PAVÓN FUENTES[4], L. LORIGADOS PEDRE[4], J. RUIZ FUENTES[5], A. DÍAZ GARCÍA[6], A. YGLESIAS RIVERA[6]
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Abstract: Synaptic plasticity requires *de novo* genes expression and protein synthesis for long lasting synaptic modificationsand behavioral changes. Previously, it has been indicated that a low glutathione content can impair short and long term synaptic plasticity mechanisms;

however,this topic remains poorly explored. The aim of the present work is to evaluate the effect of GSH depletion on synaptic plasticity of the nigrostriatalpathway. L-buthioninesulfoximineor NaClwas injected in the *substantianigracompacta* of Male Sprague Dawley rats. Arc, bdnf and D2 mRNA expression were determinedby RT-PCR at 24 hours and 7 days after BSO injection. In addition, rats were evaluated in object exploration test and TH-positive cells were counted at 7 days. Results showed lower exploration in BSO rats as well as loss of dopaminergic cells in the SNpccomparing to controls. No modifications in bdnf or arc mRNA expression were found in the SNpc but both genes increased their expression in the striatum. Moreover, the expression of D2 receptor was decreased in the SNpc and increased in the striatum. Taken together, these results suggest that transient GSH depletion is related to impairment of exploratory behavior by means of nigral degeneration and nigrostriatal plasticity modifications.

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Poster

689. Subcortical Physiology and Regulation of Behavior

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Topic: E.03. Basal Ganglia

Support: NIH Grant R01DA041705

Title: Calcium-dependent potassium currents can promote or inhibit burst firing depending upon their temporal dynamics

Authors: *C. J. KNOWLTON, C. C. CANAVIER
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Abstract: Midbrain dopamine neurons are implicated in the many known disorders of dopamine signaling including addiction, schizophrenia and Parkinson's disease. In vivo, they exhibit two primary activity patterns, tonic (single spike) firing and phasic bursting. These firing patterns, and the transitions between them, are essential for driving release of dopamine, and thus for controlling signal processing and behavioral functions of cortico-striatal circuits. Two potassium currents, the small conductance (SK) calcium-activated potassium current and the ATP-mediated potassium (K-ATP) current have been shown to have opposite effect on bursting in nigral dopamine neurons. Blocking the SK current de-regularizes firing and increases bursting (Drion et al. PLoS Comput Biol. 7:e1002050 2011), whereas silencing K-ATP channels, using virally mediated gene transfer, greatly reduces burst firing in a medial subpopulation of these neurons (Schiemann et al. Nature Neuroscience 15:1272, 2012). This result seems paradoxical in light of

the putative indirect Ca^{2+}-dependence of the K-ATP channel (Knowlton et al. SFN abstract 246.03, 2016): why would two calcium-dependent potassium currents have diametrically opposed effects on bursting? In order to address this question, we used a separation of time scales approach. Our simple one-compartment model has a fast subsystem for spiking, comprised of a voltage-dependent Na^+ current and a delayed rectifier K^+ current. It also includes a low threshold voltage-dependent Ca^{2+} current and a calcium balance that provided two slow variables: the free Ca^{2+} concentration which activates the SK channel, and a delayed version of the Ca^{2+} signal implemented with a first order differential equation. This delayed version is an analog for the ADP/ATP metabolism that activates the K-ATP channels. Experimental studies to date have not been designed to study the effects of SK and K-ATP block on bursting in the same neuron. We demonstrate that both effects could theoretically be observed in the same neuron; when a random barrage of EPSPs with an NMDA component was incorporated, the model was able to mimic both the increase in bursting due to SK block and the decrease in bursting due to K-ATP block. In a deterministic version of the model, 1) both types of bursting are initiated by a fold bifurcation, 2) bursting mediated by SK reduction is terminated by a flip bifurcation, whereas 3) K-ATP mediated bursting is terminated by a homoclinic bifurcation. These results resolve the paradoxical effects of these currents and suggest that burst signaling in nigral dopaminergic neurons is heterogeneous.

Disclosures: C.J. Knowlton: None. **C.C. Canavier:** None.

Poster

689. Subcortical Physiology and Regulation of Behavior

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Topic: E.03. Basal Ganglia

Support: Fondecyt 1141170

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Title: Axon initial segment morphology can account for variability in the intra and extracellularly recorded action potentials in nigral dopamine neurons

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Abstract: For over three decades, action potentials (APs) in nigral dopamine neurons have been thought to have two separate components, reflecting initiation in the axon initial segment (AIS)

and subsequent somatic dendritic (SD) spike. This is evidenced as a notch in the extracellular waveform and in the derivative of the intracellular waveform recorded in the soma (Grace AA and Bunney BS, 1983). The two components are often visible in the phase plane in which the membrane potential is plotted versus its first temporal derivative (Bean BP, 2007). However, the two separate components are not observed in all recordings from these neurons (Lerner et al, 2015). Here, we use a morphologically realistic model of a pacemaking nigral dopamine neuron to dissect the contribution of these two components to both the intra and extracellularly recorded waveforms. It is known that spontaneous firing rate of dopaminergic neurons depends on the relative size of their AIS (Meza, López-Jury, Canavier and Henny, in revision) and we wanted to know if this morphological variable also affects the AP waveform. Decreasing the length of the AIS makes the AIS component in the phase plane less prominent, to the point where it can disappear. Location, on the other hand, does not seem to affect the prominence of the AIS component. Electrophysiology studies shows that the shape of the extracellular waveforms is well correlated with the first differential of the intracellular waveforms on dopaminergic neurons (Ungless MA and Grace AA, 2012). In our model, for an active soma indistinguishable from the dendrites, no notch appears in the extracellularly recorded AP, despite it does in the intracellular AP. However, if the axial currents overwhelm the intrinsic somatic currents, then separate AIS and dendritic components are visible in the extracellularly recorded AP and the notch appears. In this case, the extracellular AP is proportional the derivative of the intracellularly recorded AP. We also tested, for this case, the effects of AIS length on extracellular AP shape. The notch increases its amplitude with increasing AIS length. Thus these results explain how the morphology of the AIS can explain much of the observed variability in intracellular and extracellular AP waveforms.

Disclosures: L.F. Lopez Jury: None. **R. Meza:** None. **C.C. Canavier:** None. **P. Henny:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

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Program#/Poster#: 690.01/JJ3

Topic: E.03. Basal Ganglia

Title: Conditional knockdown of Slitrk-1 gene in striatal cholinergic interneurons impairs sensorimotor function in mice mimicking Tourette syndrome

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Abstract: The Slitrk-1 (*Slit and NTrk-like family 1*) gene is one of vulnerable risk genes in Tourette syndrome (TS), a chronic neuropsychiatric disorder with multiple motor and phonic tics regarded as stereotyped behaviors. In the striatum of mammals, Slitrk-1 is highly expressed in early childhood but gradually disappeared in adulthood except cholinergic interneurons, which are the only striatal neurons with persistent expression of Slitrk-1 into adult stage. A postmortem study had shown that adult TS patients had less cholinergic interneurons in the striatum than normal subjects, suggesting the contribution of Slitrk-1 in maintaining normal function of striatal cholinergic interneurons in adults. We, therefore, hypothesized that silencing Slitrk-1 in the striatum of adult mice can be an animal model of TS by impairing the function of striatal cholinergic interneurons specifically, leading to certain stereotyped behaviors. Slitrk-1 siRNA or non-targeting scramble siRNA (*Accell siRNA*) was bilaterally injected (0.5 μg in 0.5 μl) into the dorso-medial striatum (A:-0.74mm, L:±1.6 mm, D: 3.5 mm) of C57Bl/ 6J mice (8-10 weeks). A serial analysis of mice behaviors and prepulse inhibition (PPI), a TS endophenotype, was performed after injection of siRNA for 72 hours. Mice with Slitrk-1 siRNA injection (Slitrk-1-KD, n=6) showed significantly more stereotyped behaviors, compared to those with scramble siRNA (n=6), and these stereotyped behaviors were suppressed significantly by haloperidol (0.3mg/kg, *i.p.*), an effective anti-tic agent by blocking D2 receptors (n=4). The Slitrk-1-KD group had obviously impaired PPI (n=3), as compared with the scramble group (n=3). Adhesive removal test, another test for evaluation of sensori-motor function, was also performed by measuring the latency to remove the adhesive patch on forepaws. The Slitrk-1-KD group (n=6) showed longer latency than the scramble group (n=5) (119.0±33.3 v.s. 36.4±6.2 sec, p=0.04), which means the Slitrk-1-KD group had sensori-motor impairment. Electrophysiological characteristics of the Slitrk-1 KD cholinergic (ChAT) interneurons were also examined. Slitrk-1 KD ChAT interneurons seemed to have the trend showing higher action potential threshold and decreased firing rate under step stimulations, implying the function of ChAT interneurons may be impaired. These results revealed selective knockdown Slitrk-1 gene in the striatal ChAT interneurons of adult mice, inducing haloperidol-sensitive excessive stereotypy behaviors, impaired PPI, longer adhesive removal time and altered electrophysiological characteristics of ChAT interneurons, could be regarded as an animal model of TS.

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Poster

690. Corticostriatal and Pallidal Physiology

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Topic: E.03. Basal Ganglia

Support: NSERC Discovery Grant

Canadian Foundation for Innovation

Title: Investigation of subpallial neural circuits in larval zebrafish

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[2]Univ. of Toronto Scarborough, Toronto, ON, Canada

Abstract: Neural circuits in the basal ganglia play a central role in determining what actions we perform, however, much remains unknown concerning the circuit mechanisms within these structures that underlie behavioral decisions. Remarkably, it has recently been shown that the majority of the components and connections of the mammalian basal ganglia are present in the ancient jawless lamprey, indicating that they are also likely to be present in teleosts. If these circuits exist, the reduction in complexity and unparalleled optical access in larval zebrafish, when compared to the attributes of rodent models of basal ganglia function, should make relationships between basal ganglia activity and behavioral control more salient. To address the function of basal ganglia circuits in zebrafish, we are utilizing Gal4 lines that target the fish's putative direct and indirect pathways which have been shown in mammals to promote or inhibit movement respectively. To gain genetic control of the indirect pathway, we are using a BAC transgenic line which stably expresses Gal4 in neurons that express the dopamine receptor gene drd2a (generated in a Baier Lab BAC screen). For the direct pathway, we are targeting Gal4 to the drd1a locus using CRISPR/Cas9 integration and are currently screening for stable lines. Following anatomical characterization of the drd2a and drd1a Gal4 lines, we will examine the function of labeled circuits using a combination of population calcium imaging, pharmacology, optogenetics and behavioral analyses. By taking this multifaceted approach, we should be able to identify the logic of cellular activity patterns throughout the direct and indirect pathways of larval fish and hopefully provide new insights into general circuit mechanisms controlling action selection across species.

Disclosures: T. Thiele: None. **H. Chasiotis:** None. **M. Martin:** None. **V. Aguda:** None. **N. Guilbeault:** None.

Poster

690. Corticostriatal and Pallidal Physiology

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GRSNC

Title: Globus pallidus activity during short-term adjustments of the speed-accuracy trade-off in a reach selection task

Authors: *D. THURA, P. CISEK
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Abstract: The basal ganglia (BG) have long been implicated in many aspects of cognition and motor control. Previous theoretical and experimental work suggests that they play a role in the adjustment of the speed-accuracy trade-off (SAT) of decisions between conditions favoring either hasty or accurate decisions. Our previous results (SFN 2015, 2016) are consistent with that proposal, suggesting that SAT adjustment occurs through modulations of a context-dependent urgency signal originating from the BG to regulate decision-related activity in cortical structures. However, in addition to adjustments between different contexts, humans and animals also exhibit SAT adjustments on a shorter time-scale, within each context, depending on the outcome of previous trials. Here, we investigate whether the BG are involved in such short-term SAT adjustments.

To investigate this question, we recorded pallidal activity in two monkeys trained to perform a probabilistic decision task in which sensory evidence guiding the decision continuously evolves during the time course of trials. Animals were free to report their choices by moving a cursor whenever they felt confident enough to commit. We first compared neural activity in trials following a correct choice versus those following an error. We found that in the globus pallidus externus (GPe) and internus (GPi), very few cells varied their baseline activity depending on the previous trial outcome. This contrasts with our findings in dorsal premotor and primary motor cortex (Thura et al. 2017 J Neurophysiol), in which roughly half of the population showed either higher or lower activity depending on previous trial outcome. Next, we computed the outcome history in sequences of 10 trials and investigated if more vs. less successful sequences affected GP responses in the next trial. Here again, we found only a small minority of cells showing modulation of baseline activity depending on performance history. Finally, we compared the baseline activity of BG cells averaged across 5-10 trials and compared it against the animal's success probability and decision timing averaged across the same trials. We found that baseline activity of 30-50% GP cells significantly co-varied with the monkey's decision duration and/or success probability. These results suggest that BG activity reflects the speed-accuracy trade-off of decisions before the influence of sensory evidence, and that this fluctuates on a time scale of a few trials as well as between different behavioral contexts.

Disclosures: D. Thura: None. **P. Cisek:** None.

Poster

690. Corticostriatal and Pallidal Physiology

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Topic: E.03. Basal Ganglia

Support: PAI 7/10

BELSPO

FNRS

Title: Specific gene deletion in the efferent striatal pathways confer electrophysiological, neuronal morphological and behavioural characteristics of ASD in mice

Authors: *D. RIAL[1], E. PUIGHERMANAL[2], E. VALJENT[2], S. N. SCHIFFMANN[1], A. D. D'EXAERDE[1]
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Abstract: Keywords: Striatum, cell-type-specific gene, striatonigral pathway.
The striatum is a critical brain structure for motor programming, attention, motivation, action selection and cognitive flexibility. The striatum is mainly composed by neurons denominated MSNs (medium spiny neurons) driven by cortico-thalamic projections that based on their function and neurochemical phenotype are traditionally divided into two distinct populations, namely the striatonigral and the striatopallidal pathways; these populations give rise to the direct (expressing dopamine D_1 receptors, D_1R) and indirect pathways (expressing adenosine A_{2A} receptors, $A_{2A}R$). Still the striatum can be divided in subregions namely the dorso-medial, dorso-lateral and ventral striatum (DMS, DLS and VS respectively). Each of these subregions is accounted for different functions receiving input from distinct brain regions. A clear overlap between striatal functions and correlated symptoms of ASD, such as stereotyped routines, rigid thinking and abnormal social approach would involve dysfunctions of the DMS, DLS and VS respectively (Fuccillo, 2016). The involvement of the striatum as a whole indicates a rationale role for the intertwinned cell-selective disruption in the physiological functions within the striatum. Comparative analysis in rodents provides a unique opportunity to leverage growing genetic association data to reveal whose dysfunction directly contributes to aspects of ASD symptomatology. Here we intent to identify and functionally characterize genes expressed in both pathways that could mimic ASD-like symptoms in electrophysiological, behavioral and neuronal morphological aspects in mice. Using flox mice we generated knockout models for these genes. We are now assessing the effect of gene deletion using a multi technique approach,

combining 3D reconstruction, electrophysiology and behavioral tests.
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Disclosures: D. Rial: None. **E. Puighermanal:** None. **E. Valjent:** None. **S.N. Schiffmann:** None. **A.D. d'Exaerde:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 690.05/JJ7

Topic: E.03. Basal Ganglia

Support: "Non-linear Neuro-Oscillology" from the MEXT.

Title: Correlated activity in globus pallidus neurons of a macaque monkey during hand reaching movements

Authors: *W. WONGMASSANG, S. CHIKEN, T. HASEGAWA, A. NAMBU
Div. of Syst. Neurophysiol., Natl. Inst. For Physiological Sci., Aichi, Japan

Abstract: The basal ganglia (BG) are a group of subcortical nuclei, which play a crucial role in control of voluntary movements. There are many reports on movement-related activity in the external (GPe) and internal (GPi) segments of the globus pallidus; the former sends inhibitory signals to multiple BG nuclei and may control the whole BG activity, whereas the latter sends inhibitory BG outputs to the thalamo-cortical and brainstem motor systems. The correlated GPe/GPi activity may converge in the target nuclei and induce large inhibitory effects and post-inhibitory rebounds, however previous studies have reported no correlation of GPe/GPi activity at rest without tasks. In this study, we examined correlation of GPe/GPi activity during hand reaching task. A female Japanese macaque monkey (*Macaca fuscata*) was trained to perform a reaching task with its hand to the left or right target, which was indicated by LED. The activity of GPe/GPi neurons was simultaneously recorded during task performance using a multi-channel electrode with 16 equally spaced contacts by 150 μm. The bipolar stimulating electrodes were also inserted chronically into the hand area of the primary motor cortex (MI) and supplementary motor area (SMA). MI/SMA stimulation induced a triphaisc response composed of early excitation, inhibition and late excitation, suggesting that GPe/GPi neurons were located in the hand motor area. Many GPe/GPi neurons changed their activity in relation to task events, such as hand-release from the home position, reaching movements, touching the target, and reward delivery. Some GPe-GPe and GPi-GPi pairs showed short-duration but significant correlated activity at specific event timings, although most pairs showed weak or no correlation. Our findings have demonstrated that while the majority of GPe/GPi activities are functionally

independent, a fraction of them transfer neuronal information to their target nuclei by correlated activity.

Disclosures: W. Wongmassang: None. **S. Chiken:** None. **T. Hasegawa:** None. **A. Nambu:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

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Program#/Poster#: 690.06/JJ8

Topic: E.03. Basal Ganglia

Support: Israel Science Foundation (ISF) grant (743/13)

Title: Behavioral and neuronal correlates of hyperactivity in the nucleus accumbens disinhibition rat model

Authors: *D. YAEL, I. BAR-GAD
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Abstract: Attention deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder affecting roughly 5% of children with persistence of 30-50% in adulthood. While the pathophysiology leading to ADHD is unknown; multiple lines of evidence suggest the involvement of the cortico-basal ganglia pathway, and particularly fronto-striatal networks. In this study, we present a novel rodent model in which hyperactivity is elicited by disinhibition of the nucleus accumbens (NAc). Following injections of a GABA-A antagonist (bicuculline) into the NAc, the animals developed hyperkinetic symptoms expressed as increased locomotion lasting for 30-45 minutes. The neuronal activity of the behaving rat's dorsal and ventral striatum was continuously recorded during naïve and hyperactive states and their behavior was monitored. The behavior of the animals was offline analyzed, and their movement was automatically tracked. Kinematic properties were extracted from the data and synchronized with the recorded neuronal activity. Comparison between the naïve and disinhibited states reveals qualitative and quantitative changes in the neuronal activity in both the macro (local field potential) and micro (single neurons) scales. In addition, comparison of the bicuculline injections into the NAc to those performed into the dorsal striatum, which elicit motor tics, reveals common changes in the neuronal encoding in the limbic and sensorimotor territories. Our data provides new insights into the involvement of the limbic basal ganglia in the expression of hyperactivity and normal motor behavior.

Disclosures: D. Yael: None. **I. Bar-Gad:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 690.07/JJ9

Topic: E.03. Basal Ganglia

Title: Rostral thalamic intralaminar nuclei modulation of striatal microcircuitry and action

Authors: *K. K. COVER[1], U. GYAWALI[1], A. E. MARQUARDT[1], C. MU[1], M. H. PATTON[1], M. G. WHITE[1], B. M. ROBERTS[2], B. N. MATHUR[1]
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Abstract: Survival in a rapidly-changing environment requires attention to sensory stimuli in order to optimize action for reward acquisition. How specific neural circuits subserve this complex function is unclear. The thalamic intralaminar nuclei (ILN) are positioned to receive salient sensory stimuli and to directly modulate actions through a direct projection to the dorsal striatum, a critical node for action selection. The rodent ILN are distributed in caudal and rostral groupings: the caudal ILN consists of the parafascicular (Pf) nucleus, whereas the rostral ILN (rILN) includes the centromedial (CM), paracentral (PCN), and centrolateral nuclei (CL) nuclei. While the Pf has been functionally examined for its role in sensory-cued action encoding, the rostral ILN has been largely ignored. Using optogenetics and fast scan cyclic voltammetry in mice, we have identified a unique microcircuit by which the rILN innervate the dorsal striatum to elicit dopamine release. How the rILN encode sensory stimuli and cognate action selection is explored using an all-optical approach. Our results provide novel insight into how the thalamus may contribute to salience-informed action selection, which has implications for several disorders of action including Parkinson's disease and addiction.

Disclosures: K.K. Cover: None. **U. Gyawali:** None. **A.E. Marquardt:** None. **C. Mu:** None. **M.H. Patton:** None. **M.G. White:** None. **B.M. Roberts:** None. **B.N. Mathur:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 690.08/JJ10

Topic: E.03. Basal Ganglia

Title: Regulation of locomotion by nucleus accumbens core activity

Authors: *Q. YAN, H. YIN
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Abstract: Despite an extensive literature on the neural basis of locomotion in many species, the role of the brain in regulating locomotion remains poorly understood. Previous studies have indicated a critical role of the nucleus accumbens core (NAcc) in locomotion and approach behavior. Here we used optogenetics and continuous 3D motion capture to quantify the contributions of NAcc to locomotion in freely moving mice. We implanted bilateral optical fibers in the NAcc in mice that selectively expressed channelrhodopsin and halorhodopsin in the direct pathway projection neurons to manipulate NAcc output, and continuously recorded movements during both free locomotion and moving target pursuit. Our results suggest that the NAcc output may determine the initiation and termination of locomotion.

Disclosures: Q. Yan: None. **H. Yin:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

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Program#/Poster#: 690.09/JJ11

Topic: E.03. Basal Ganglia

Support: ARC Grant DP130101932

NHMRC Grant APP1037746

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ARC Award DE160101275

NHMRC Fellowship GNT1079561

Title: Stationary corticostriatal networks promote compression of automatic action in aging

Authors: *J. BERTRAN-GONZALEZ[1], Z. SKRBIS[2], M. R. BAILEY[3], P. D. BALSAM[4], B. W. BALLEINE[1], J. GOETZ[2], M. MATAMALES[1]
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Abstract: The acquisition of motor skills involves implementing action sequences that increase task efficiency while reducing cognitive loads. This learning capacity depends on specific

cortico-basal ganglia circuits that are affected by normal aging. Here, combining a series of novel behavioral tasks with extensive neuronal mapping and targeted cell manipulations in mice, we explored how aging of cortico-basal ganglia networks alters the microstructure of action throughout sequence learning. We found that, after extended training, aged mice displayed squeezed automatic behaviors characterized by ultrafast oligomeric action chunks that correlated with deficient reorganization of corticostriatal activity. Pharmacogenetic disruption of the D1-striatonigral subcircuit in dorsolateral striatum in young mice reproduced most age-related action features, and the introduction of an action-related feedback cue restored normal sequence structure in aged mice. Our results reveal static properties of aged cortico-basal ganglia networks that promote deficits in action automatization, something that can compromise procedural learning in aging.

Disclosures: J. Bertran-Gonzalez: None. **Z. Skrbis:** None. **M.R. Bailey:** None. **P.D. Balsam:** None. **B.W. Balleine:** None. **J. Goetz:** None. **M. Matamales:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 690.10/JJ12

Topic: E.03. Basal Ganglia

Title: Distinct roles for cortico- and thalamostriatal projections in motor skill learning and execution

Authors: *S. B. WOLFF, A. K. DHAWALE, R. KO, B. P. OLVECZKY
Harvard Univ., Cambridge, MA

Abstract: The remarkable capacity of the brain to acquire and execute motor skills depends on a distributed motor network. While many individual components have been identified, less is known about their specific roles and how they interact during learning and execution of motor skills. To address this, we train rats in a lever-pressing task which results in spatiotemporally precise movement patterns. Our previous finding that motor cortex is necessary for learning, but not for execution of this motor skill, suggests that motor cortex may act as a tutor for subcortical motor circuits during learning. A main candidate to receive this tutoring is the dorsolateral part of striatum, a major target of motor cortical projection neurons. In line with this hypothesis, we show that the striatum is indeed necessary both for the acquisition and execution of the motor skills we train. Furthermore, chronic and selective silencing of motor cortex's direct projections to the striatum, by viral and molecular strategies, prevented animals from learning the motor skill. In line with our previous lesion experiments, the same silencing did not affect skill execution when it was done after learning. We next tested the contribution to skill execution of striatum's other main input, that from thalamus. We found that chronic silencing of

thalamostriatal projections disrupted both skill execution and learning. These findings identify the striatum as a central player and suggest distinct roles for its cortical and thalamic inputs during motor skill acquisition and execution. To further dissect the interplay between these areas, we are combining transient and chronic activity manipulations with long-term electrophysiological recordings to study their activity, their mutual influence on each other and the network changes that accompany motor learning.

Disclosures: S.B. Wolff: None. **A.K. Dhawale:** None. **R. Ko:** None. **B.P. Olveczky:** None.

Poster

690. Corticostriatal and Pallidal Physiology

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: E.03. Basal Ganglia

Support: NICHD Grant RO1HD060630

Title: Recruitment of prefrontal-striatal circuit during skilled motor challenge

Authors: *S. PRATHAP[1], Z. WANG[2], Y. GUO[2], D. P. HOLSCHNEIDER[2]
[1]Neurosci. Grad. Program, [2]Psychiatry & the Behavioral Sci., USC, Los Angeles, CA

Abstract: BACKGROUND: Exercise, including treadmill running, dancing, Tai-Chi, bicycling and others, have been shown to improve cognition, particularly executive function in aging individuals, as well as delaying the onset of dementia in the cognitively impaired. These different exercise types differ in the extent of motor skill and aerobic challenge required for their execution. Prefrontal cortex (PFC) is well known to play a central role in cognition, and especially in executive function. Its importance in guiding motor learning—both during healthy aging, as well as during the neurorehabilitation of brain disorders—is less well understood. Our aim was to use functional brain mapping to compare the ability of two motor tasks to acutely engage the prefrontal-striatal circuit (PFC-Str). The two motor tasks--walking in a complex running wheel with irregularly spaced rungs or walking in a running wheel with a smooth internal surface--differed only in the extent of skill required for their execution.
METHODS: Adult rats received jugular vein catheters, and were habituated to a running wheel. Cerebral perfusion was mapped by injection of [14C]-iodoantipyrine during acute walking (6 m/min) in either the complex wheel or in the simple wheel. Regional cerebral blood flow (rCBF) was quantified by whole-brain autoradiography and analyzed in 3-D reconstructed brains by statistical parametric mapping and seed-based functional connectivity.
RESULTS: Correlation analysis with a medial PFC (mPFC, prelimbic area) seed showed significant correlations of the mPFC with the dorsomedial striatum during walking in the complex wheel that was not seen during walking in the simple wheel.

CONCLUSION: The level of skill involved in a motor training task determines the extent of functional recruitment of the prefrontal corticostriatal circuit. Our results are consistent with our earlier work that showed that 4 weeks of skilled wheel running improves functional recruitment of the PFC during horizontal treadmill walking, as well as discrete motor outcomes in a rat model of striatal dopaminergic deafferentation (Neurobiology of Disease, 2015, 77:71-87). These findings support the notion that the basal ganglia are significantly influenced by inputs from PFC, which may provide a top-down control signal for guiding the resolution of response competition that amplifies one response command and suppresses competing commands.
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Poster

690. Corticostriatal and Pallidal Physiology

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Topic: E.03. Basal Ganglia

Support: Ben & Gayle Batey Neuroscience Fund

NIH MARC USTAR Training Grant T34GM118212-01

Title: High fat diet blocks the effect of the antipsychotic haloperidol and enriched environments reverses the effect in rats

Authors: *I. C. SUMAYA, S. VILLARREAL, N. RAMIREZ, A. HUSSAIN, M. CHAUNDHRY
Psychology - 24 DDH, California State Univ. Bakersfield, Bakersfield, CA

Abstract: Antipsychotics are very effective in ameliorating the positive symptoms of schizophrenia, however, a high percentage of those treated with antipsychotics suffer from the serious motor-related extrapyramidal side effects. Specifically, these drugs show high affinity for the D_2 dopaminergic receptors in the striatum serving to block the transmission of dopamine (Seeman & Lee, 1975). Relevant to the current research are the recent finding that high-fat serves to deplete dopamine in the substantia nigra and the striatum (Morris et al., 2010), the major players in voluntary motor responses. Based on these findings, the purpose of the current investigation was to investigate the behavioral motor effects of high fat and low fat on the dopamine system during treatment with a D_2 antagonist that is used in clinical populations in the treatment of schizophrenia. Also, based on previous work done in our lab finding that enriched environments served to counteract the negative effects of high fat in cognitive domains (Suter et

al., 2016; Sumaya et al., 2015), we were also interested in investigating the possible effects of environmental enrichment on motor domains after treatment with a D_2 antagonist. We placed rats in either enriched environments (n=20) or standard cages (n=20) and fed rats either a low fat diet (10% fat) or a high fat diet (45% fat) for a month then injected rats with the dopamine antagonist, haloperidol (1 mg/kg, i.p). We then tested rats in the bartest measuring hypokinesia. Our controls, the low fat group housed in regular cages, experienced high levels of hypokinesia staying on the bar for an average of 18 minutes (1090 $\pm$238.50 sec). However, their counterparts fed a high fat diet experienced little to no hypokinesia only staying on the bar for an average of 17 seconds (17.10$\pm$4.37 sec) thus showing high fat to counteract the effect of haloperidol. Paradoxically, rats in the enriched environments fed a high fat diet experienced high levels of hypokinesia (587.40$\pm$203.82). Similar to the groups in the regular cages, the low fat groups in the enriched environments also showed high levels of hypokinesia (928.20$\pm$255.06 sec). In regards to weight, as expected, rats fed the high fat diet gained more weight as compared to the low fat group and regardless of diet, rats in enriched environments gained the least amount of weight. In summary, the high fat diet served to counteract the effects of haloperidol and enriched environments served to reverse the effect. These results provide first time behavioral data showing high fat diets to interfere with the effects of antipsychotics and that the environment may play a role in these effects.

Disclosures: I.C. Sumaya: None. **S. Villarreal:** None. **N. Ramirez:** None. **A. Hussain:** None. **M. Chaundhry:** None.

Poster

690. Corticostriatal and Pallidal Physiology

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Program#/Poster#: 690.13/JJ15

Topic: E.03. Basal Ganglia

Title: Short term plasticity shapes information transmission in the indirect pathway of the rat basal ganglia

Authors: *H. LAVIAN[1], A. KORNGREEN[1,2]
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Abstract: The basal ganglia have long been implicated in motor control and action selection. During movement, cortical information flows through the basal ganglia via the direct, indirect and hyper-direct pathways, and converges to the entopeduncular nucleus (EP), one of the basal ganglia output nuclei. In the indirect pathway of the basal ganglia, globus pallidus (GP) neurons form inhibitory depressing synapses in the EP. GP neurons are spontaneously active and show transient decreases or increases in firing rate during movement. Inputs from the indirect pathway

continuously modulate the firing of EP neurons, yet the link between these synaptic inputs to neuronal firing in the EP is unclear. To investigate this input-output transformation we used numerical modeling and whole cell recordings from single neurons in rat brain slices. First we constructed a model of an EP neuron that receives input from a constantly active inhibitory depressing synapse. We used this model to predict the change in EP membrane potential induced by transient changes in firing rate of the presynaptic neuron. Our simulations show that the change in EP membrane potential, and subsequent firing rate, depends greatly on the initial activation frequency of the synapse. We further performed whole cell recordings from single neurons in the EP and recorded the response to stimulation of the GP at different frequencies. These recordings yielded similar results to those of the simulations, showing that integration of GP evoked inhibitory post synaptic potentials depends both on the present and past firing rate of the presynaptic neuron. Our results thus show that the inhibitory effect of GP input on EP activity is highly dependent on the baseline frequency of the pallidal neurons, and demonstrate how short term synaptic plasticity shapes information transmission through the indirect pathway of the basal ganglia.

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Poster

690. Corticostriatal and Pallidal Physiology

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Topic: E.03. Basal Ganglia

Support: RFBR Grant 15-04-05313

Title: Differences in globus palllidus asymmetry in patients with cervical and generalized dystonia

Authors: *A. SEDOV[1], S. USOVA[1], U. SEMENOVA[1], V. POPOV[2], R. MEDVEDNIK[1], A. TOMSKIY[2], A. G. SHAIKH[3]
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Abstract: Dystonia is a movement disorder defined by sustained muscle contractions, causing twisting and repetitive movements and abnormal postures. The pathophysiology of dystonia is incompletely understood, but it is thought to involve the loop circuit from sensorimotor cortices (SMC) through parts of the basal ganglia and ventrolateral thalamus and back to cortex. The globus pallidus internus (GPi) occupies a critical position in this circuit, being the major output structure of the basal ganglia “motor” territory. Decreases and increases in discharge of the

GABAergic neurons of GPi are believed to facilitate and suppress, respectively, the activity of recipient thalamocortical circuits and, eventually, muscle activity. Asymmetric pallidal neuronal activity was shown in patients with cervical dystonia.We used microelectrode recording (MER) and local field potentials (LFP) to analyze the differences of pallidal asymmetry in patients with cervical and generalized dystonia. The data was obtained during microelectrode-guided basal ganglia stereotaxic DBS surgeries. We used burst index to separate tonic and burst cells and calculate mean firing rate. We also perform spectral analysis of LFP and estimate oscillations scores (OS) for each band: delta, theta, alpha, beta and gamma. We found that discharge rate of GPi tonic cells was significantly higher in ipsilateral to the side of head turning or tilt in CD patients. In GD patients we found just few tonics cells. At the same time, GPi burst cells have the same discharge rate for both side in CD and GD patients. LFP analysis has shown the asymmetry in gamma range oscillation scores in CD and no asymmetry in GD patients. It is worth noting the absence of any interhemispheric differences in GPe activity for all patients. Imbalance in GPi tonic cells activity could influence on the level of thalamic activity and thus results in imbalance in neck muscle activity. Our data confirm the hypothesis that CD is associated with an asymmetric pallidal outflow and imbalance in direct pathway. We propose that GPi asymmetry could be results from disturbance of proprioceptive feedback or cerebellar motor efference copy.

Disclosures: **A. Sedov:** A. Employment/Salary (full or part-time):; Semenov Institute of Chemical Physics Russian Academy of Sciences. 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.; Russian Foundation for Basic Research, grant RFBR 15-04-05313. **S. Usova:** None. **U. Semenova:** None. **V. Popov:** None. **R. Medvednik:** None. **A. Tomskiy:** None. **A.G. Shaikh:** None.

Poster

690. Corticostriatal and Pallidal Physiology

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Program#/Poster#: 690.15/JJ17

Topic: E.03. Basal Ganglia

Support: R01NS052318

R01NS075012

T32NS082169

Z01-AG000949-0

Title: Parkinson's disease risk genetic polymorphisms are associated with imaging markers of the putamen and substantia nigra in healthy adults

Authors: *D. E. VAILLANCOURT[1], R. G. BURCIU[2], P. SHUKLA[3], M. NALLS[5], A. SINGLETON[5], M. OKUN[4], R. D. SEIDLER[6]
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Abstract: Great efforts are being made towards developing new approaches to assess which people are at greater risk for developing Parkinson's disease (PD). While genetics and neuroimaging offer distinct possibilities for determining those at risk for developing PD, a combined approach may offer even greater insight. In this study, we used a neurogenetics approach to explore two neuroimaging biomarkers for PD in a group of healthy adults that carry risk variants for developing PD. A total of 31 individuals with no motor and cognitive symptoms (mean age: 62.1 ± 9.3; 14 males) participated in the study. Functional magnetic resonance imaging (fMRI) during a force production task and diffusion magnetic resonance imaging (dMRI) with 64 directions were performed on a 3T Philips Achieva scanner equipped with 32-channel headcoil. The primary outcome measures were percent signal change in the putamen and free-water in the substantia nigra. We also collected clinical data using the following tests: motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale, Purdue Pegboard Test, Dynamic Gait Index, 6-Minute Walking Test, Montreal Cognitive Assessment, and Beck Depression Inventory. Participants were genotyped using the NeuroX platform and and two commonly cited single nucleotide polymorphisms that have been associated with increased odds risk of PD were examined: rs356219 and rs76904798 that relate to the SNCA and LRRK2 genes, respectively. In our analysis we summed across the two variants and ended with a value between 0-2 for each control subject, with 2 representing the highest value indicating a person is a carrier of both risk variants. Results showed that the number of "at-risk" genotypes was significantly associated with reduced fMRI signal in the putamen, and elevated free-water in the anterior substantia nigra. There was no association between the number of "at-risk" genotypes and clinical measures. Together, results suggest that healthy individuals who carry multiple risk variants for PD have impaired nigrostriatal function and structure. Task-fMRI and dMRI markers represent brain endophenotypes for carriers of PD risk genotype loci, which could open the door for a neurogenetics approach in prodromal PD.

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Poster

690. Corticostriatal and Pallidal Physiology

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Topic: E.03. Basal Ganglia

Support: National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, Division of Intramural Clinical and Biological Research (DICBR)

Title: Electrophysiological and behavioral characterization of a mutant mouse lacking Rem2 protein in striatal medium spiny neurons

Authors: *D. J. LIPUT[1], H. L. PUHL, III[3], S. R. IKEDA[2]
[1]Lab. of Mol. Physiol., [2]Lab. Molec Physiol., NIH/NIAAA, Rockville, MD; [3]NIH, Rockville, MD

Abstract: Rem2 is a small GTPase of the Ras-related RGK family and is primarily expressed in the nervous system, including the striatum. Previous studies have shown that Rem2 inhibits high-voltage-activated Ca^{2+} channels and instructs dendritogenesis and synaptogenesis. To evaluate the role of Rem2 in the striatum, we generated a Rem2 conditional knockout mouse line and bred these animals to a RGS9cre driver line to generate mice with a deletion of Rem2 in striatal medium spiny neurons (MSN-Rem2KO mice). For some experiments, a tdTomato transgene, under the control of the dopamine D1 receptor promoter, was bred onto the MSN-Rem2KO line. To examine the effect of Rem2 knockout on synaptic input to MSNs and intrinsic excitability, acute brain slices containing striatum were prepared (> P25). Spontaneous EPSCs were recorded from MSNs in the dorsal striatum. Rem2 knockout decreased sEPSC frequency (median: 2.6 vs 1.7 Hz) and increased corresponding sEPSC interevent intervals (median: 395.4 vs 580.2 ms), but had no effect on sEPSC amplitude. Intrinsic excitability was assessed by delivering 500 ms hyperpolarizing and depolarizing current steps (-200 pA to +780 pA) and recording voltage output. Consistent with previous reports, striatopallidal MSNs were more excitable then striatonigral MSNs evidenced by lower rheobase and a leftward shift in the action potential frequency (F-I) curve. However, excitability of $MSN^{LoxP/LoxP}$ and MSNRem2-KO neurons was indistinguishable. Whole-cell calcium currents were recorded from acutely dissociated MSNs. I-V curves recorded from $MSN^{LoxP/LoxP}$ and MSN-Rem2KO neurons were similar over the entire voltage range examined (-80 mV to +75 mV). Normalized peak current density was larger in MSN-Rem2KO neurons (median: -65.2 vs -92.1 pA/pF), which was attributed to a decrease in capacitance (median: 6.8 vs 5.6 pF). The effect or Rem2 knockout on striatum dependent behavioral output was also assessed. Adult $MSN^{LoxP/LoxP}$ and MSN-Rem2KO mice had similar performance on an accelerating rotarod task and displayed equivalent locomotor activity in a novel environment. $MSN^{LoxP/LoxP}$ and MSN-Rem2KO mice learned a fixed ratio operant

conditioning task at similar rates. However, in preliminary progressive ratio experiments, MSN-Rem2KO mice (n = 6) displayed elevated lever press responses and achieved higher breakpoints compared to $MSN^{LoxP/LoxP}$ mice (n = 5). These results may be related to changes in effort as extinction was similar between genotypes in a separate cohort of mice. The results presented are consistent with the hypothesis that Rem2 is involved in striatal synaptogenesis and has a role in some domains of striatum dependent behavioral output.

Disclosures: D.J. Liput: None. **H.L. Puhl:** None. **S.R. Ikeda:** None.

Poster

690. Corticostriatal and Pallidal Physiology

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Program#/Poster#: 690.17/JJ19

Topic: E.03. Basal Ganglia

Support: Penn State Huck Institutes of the Life Sciences

Title: The thalamic posteromedial nucleus activates the direct pathway

Authors: *K. D. ALLOWAY[1], G. D. WATSON[2]
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Abstract: Clinical studies indicate that deep brain stimulation in the zona incerta (ZI) reduces the symptoms of Parkinson's disease (PD). This is significant because ZI inhibits the medial part of the posterior (POm) thalamic nucleus, which innervates only the dorsolateral part of the striatum (DLS), a basal ganglia structure that is essential for the expression of repetitive sensorimotor habits. To assess the potential influence of POm on the basal ganglia, we first used neuronal tracing combined with unbiased stereology to assess the relative strength of the projections from the dorsomedial and dorsolateral striatal regions to the external globus pallidus (GPe) and the substantia nigra pars reticulata (SNR), which are the respective targets of the Indirect and Direct pathways. Subsequently, we used optogenetic stimulation combined with extracellular recording techniques to determine whether activation of POm alters neuronal activity in the substantia nigra reticulata (SNr), which is a major output nucleus of the basal ganglia.
Consistent with previous studies, we found that anterograde tracer deposits in the dorsomedial striatum revealed equal innervation of the external globus pallidus (GPe) and SNr. By contrast, tracer deposits in the DLS indicate that its neurons project preferentially to SNr. Consistent with these anatomical results, short pulses of optical stimulation in POm caused brief activation of neuronal activity in DLS that is immediately followed by longer-lasting inhibition of neurons recorded in the lateral part of SNr. Although many neurons in SNr did not respond to POm

stimulation, we never observed POm-induced excitation in SNr. These results suggest that POm preferentially activates the direct pathway of the basal ganglia. To examine how ZI deep brain stimulation might mediate its therapeutic effects in PD, we are currently characterizing the effects of ZI electrical stimulation on neuronal activity in POm, DLS, and SNr.

Disclosures: K.D. Alloway: None. **G.D. Watson:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 690.18/JJ20

Topic: E.03. Basal Ganglia

Support: Rutgers Brain Health Institute Pilot Grant (DJM, JMT)

NIH R01 NS034865 (JMT)

NIH R01 NS094450 (DJM)

Title: Corticostriatal inputs from somatosensory and motor cortex have distinct effects on behavior through differential actions on striatal neurons

Authors: *C. R. LEE[1], J. M. TEPPER[2], D. J. MARGOLIS[1]
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Abstract: The striatum is the main input nucleus of the basal ganglia and receives excitatory afferents from wide areas of neocortex as well as the thalamus. It is largely unknown, however, whether 1) afferent input from sensory and motor cortical areas has different effects on behavior and 2) how distinct areas of cortex influence striatal projection neurons and interneurons. Here, we explored the roles of primary somatosensory cortex (S1) and primary motor cortex (M1) in controlling behavior and the cellular mechanisms that might underlie those functions. Specifically, we tested the hypothesis that corticostriatal input from S1 induces sensory-driven behavioral response inhibition while input from M1 promotes behavioral response activation. Channelrhodopsin-2 (AAV1.CamKIIa.hChR2(H134R)-eYFP.WPRE.hGH) was expressed in either S1 or M1 and mice were trained to perform a tactile Go/No-Go decision making task using their whiskers to discriminate between two textures for a water reward. Preliminary results indicate that activation of S1 inputs to striatum increased the number of trials without a response (correct reject and miss) while activation of M1 inputs to striatum increased trials with a response (hit and false alarm).
We investigated the possible cellular mechanisms underlying these behavioral effects using ex vivo whole cell recordings of identified D1 and D2 receptor-expressing medium spiny neurons

as well as parvalbumin (PV)-expressing fast spiking interneurons and optogenetic activation of corticostriatal afferents from S1 or M1. These experiments revealed marked differences in the amplitude of excitatory postsynaptic potentials (EPSPs) recorded in each of the neuron types from the two cortical areas. Optogenetically activated inputs from S1 to striatum induced an approximately 7-fold larger EPSP in PV-expressing interneurons when compared to either D1 or D2 receptor-expressing medium spiny neurons. In contrast, optogenetic activation of M1 corticostriatal inputs produced an an EPSP of similar amplitude in D1 and D2 medium spiny neurons as well as PV-expressing interneurons.
Our results suggest that corticostriatal input from S1 and M1 induces behavioral inhibition and activation respectively, that is likely mediated through distinct activation of striatal circuitry by these cortical regions.

Disclosures: C.R. Lee: None. **J.M. Tepper:** None. **D.J. Margolis:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 690.19/JJ21

Topic: E.03. Basal Ganglia

Title: Corticostriatal projections map the organization of inter-area corticocortical connectivity

Authors: *A. E. PAPALE[1], R. PALETZKI[2], M. FEROZE[1], C. R. GERFEN[2], B. M. HOOKS[1]
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Abstract: A long standing model of corticostriatal organization is that interconnected cortical areas form the basis of parallel functional circuits through the basal ganglia. This model accounts for both the topographic organization of corticostriatal projections as well as the patterns within the striatum from different cortical areas. An emerging view ascribes distinct functions in motor behavior to dorsolateral, dorsomedial and ventral striatal regions. To better understand how the information responsible for these distinct functions is organized, we analyzed the projections of layer-specific subtypes of cortical projection neurons in primary somatosensory, primary motor and secondary motor cortical areas. Mice with Cre-expression selective for intratelencephalic layer 5A (IT), pyramidal tract layer 5B (PT), and corticothalamic layer 6A (CT) were injected with 3 different Cre-dependent reporter viral vectors in different cortical areas. After sectioning and imaging of brains, images were aligned to a reference brain using BrainMaker software (MBF Bioscience). For each Cre-driver line, up to 90 injection sites were analyzed. Long-range axonal projections in specific target regions were then assessed. Correlation coefficients of voxel fluorescence in striatum were computed across injection sites. A hierarchical clustering algorithm was applied to the correlations, revealing distinct clusters that were well-matched to

injection sites. In striatum, primary motor and sensory areas clustered together, as did medial and lateral frontal cortical areas. Analysis of correlations along different anatomical dimensions suggested a distinct anterior/medial region of striatum where all areas of the sensorimotor system converge. Comparison of topography for IT- and PT-projections to striatum revealed differences in the degree of topographic precision. K-means clustering analysis of striatum suggested subdivision of striatum that corresponded well with expected regions given known striatal connectivity. In conclusion, we find that subcortical projections from sensorimotor areas are coarsely topographic, allowing for integration from multiple regions in basal ganglia-thalamus-cortex loops.

Disclosures: **A.E. Papale:** None. **R. Paletzki:** None. **M. Feroze:** None. **C.R. Gerfen:** None. **B.M. Hooks:** None.

Poster

690. Corticostriatal and Pallidal Physiology

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Topic: E.03. Basal Ganglia

Support: The European Horizon2020 Framework Programme under grant agreement n°720270 (Human Brain Project SGA1)

The Swedish Research Council

NIAAA (grant 2R01AA016022)

Title: Significance of striatal feedforward inhibition in propagation of cortical oscillations

Authors: *J. BELIC, A. KUMAR, J. HELLGREN KOTALESKI
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Abstract: The basal ganglia (BG) comprise the largest subcortical system in the brain and play a crucial role in motor control and cognitive processes. The striatum is the largest and main input nucleus of the BG, receiving glutamatergic inputs from all cortical areas and thalamus. About 95% of neurons in the striatum are medium spiny neurons (MSNs) that form the only output from the striatum. Two of the most examined sources of GABAergic inhibition into MSNs are the feedback inhibition from the axon collaterals of the MSNs themselves, and the feedforward inhibition via the small population (1-2% of striatal neurons) of fast-spiking interneurons (FSIs). Feedforward inhibition is a common property of neuronal networks throughout the brain and plays a crucial role in neural computations. For instance, feedforward inhibition sets the window of temporal integration and spiking and thereby contributes to the control of firing rate and correlations. In the striatum despite their high firing rates, FSIs do not seem to play a major role

in controlling the firing of MSNs and so far, it has not been possible to attribute a functional role to FSIs in the striatum. Here, we propose that FSIs can perform an important role in transferring cortical oscillations to the striatum.
Recently, high frequency oscillations have been observed at the level of individual MSNs firing and local field potential in the striatum of both awake and anaesthetized animals. It is quite likely that the experimentally observed oscillations in the striatum are in fact cortical oscillations transmitted by the cortico-striatal projections because recurrent connectivity within the striatum is not strong enough to generate local oscillations. However, there is limited knowledge about the exact nature of this routing process and here we use a spiking neuron network model of the striatum to isolate the mechanisms underlying the transmission of cortical oscillations to not only the MSNs that receive direct cortical inputs but also to the other unstimulated MSNs. We show that the selective activation of striatal FSIs via oscillatory inputs could successfully entrain the MSN population to oscillate at the input driving frequency. Strong and divergent connectivity of FSIs implies that even weak oscillations in FSI population activity can be spread to the MSN population. Overall, our results support the idea of the precise orchestration of FSI activity that plays a key role in determining the pattern of the firing of MSNs, which might provide optimal integration of external inputs into striatal network.

Disclosures: J. Belic: None. **A. Kumar:** None. **J. Hellgren Kotaleski:** None.

Poster

690. Corticostriatal and Pallidal Physiology

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Program#/Poster#: 690.21/JJ23

Topic: E.03. Basal Ganglia

Support: ANR-10-PDOC-0016

ParisCity-DDEEES 2014-166

Title: Correlation between song acoustics and neural activity in the song-related basal-ganglia-thalamo-cortical circuit in songbirds

Authors: *A. LEBLOIS[1], W. E. WOOD[1], R. DARSHAN[2], D. HANSEL[1]
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Abstract: The ability to generate variable movements is essential for learning and adjusting complex behaviors. This variability has been linked to the temporal irregularity of neuronal activity in the central nervous system. However, how this neuronal irregularity actually translates into behavioral variability is unclear. We combine modeling, electrophysiological and behavioral studies to address this issue. A model circuit comprising topographically organized and strongly

recurrent neural networks can autonomously generate irregular motor behaviors, as recently published by our group. Accordingly, simultaneous recordings of neurons in singing finches that reveals an increase in neural correlations across the circuit driving song variability, in agreement with the model predictions. Going beyond neural correlation predicted by our modeling study, we have investigated correlations between neural activity and behavior along this pathway. Interestingly, the singing-related activity of single neurons in the premotor nucleus (Lateral Magnocellular Anterior Nucleus, LMAN) displays relatively little correlation to the acoustic features of the song syllables (pitch, spectral entropy and amplitude). In contrast, we confirm the mild but reliable level of correlation between the activity of motor neurons in the robust nucleus of the arcopallium (RA) and these acoustic features. These differences in correlation with behavior can be well explained in our network model. However, these results may challenge the recently proposed framework for the implementation of reinforcement learning in the song-related BG-thalamo-cortical loop.

Disclosures: **A. Leblois:** None. **W.E. Wood:** None. **R. Darshan:** None. **D. Hansel:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

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Program#/Poster#: 690.22/JJ24

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant RO3MH104851

NIH Grant R03AG052120

LA Regents Grant RCS-RD-A-09

Title: Distribution of interneurons associated with perineuronal nets in the mouse neocortex

Authors: R. SULTANA, *C. C. LEE
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Abstract: Perineuronal nets (PNNs) are lattice-like accumulations of extracellular matrix components surrounding the neuronal cell body, dendrites and axons, but sparing the synapse. Whereas the association of PNNs with neurons has been described for various regions of the brain, the comparative occurrence of PNNs around interneurons throughout the brain has received less attention. In the present study, we examined the distribution of PNN-associated interneurons throughout the mouse neocortex, as well as systematically and comparatively analyzed the relationship between the location and function of the differential presence of these extracellular structures. We utilized a transgenic VGAT-Venus mouse strain to identify interneurons associated with Wisteria Floribunda Agglutinin (WFA)-stained PNNs. Our study

revealed that WFA stained-PNNs were associated more commonly with interneurons in layers II/III and V/VI of mouse neocortex. However, their density was considerably different between various cortical areas, greatest in the visual cortex and fewest in the secondary motor cortices. Further analysis indicated that the neuron associated matrix sheaths around interneurons are denser in certain cortical as compared to others. Subfields of cortical areas also differed with respect to the occurrence of PNN-associated interneurons, and the subtlety of cortical representations correlated with the density of PNNs around interneurons in the primary somatosensory, motor or secondary association areas. Thus, the functional heterogeneity of different cell population in different areas of brain is reflected in the density of PNN-associated neurons.

Disclosures: R. Sultana: None. **C.C. Lee:** None.

Poster

690. Corticostriatal and Pallidal Physiology

Location: Halls A-C

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Program#/Poster#: 690.23/JJ25

Topic: B.09. Physiological Properties of Neurons

Support: G12MD007583

GM084854

(NSF) OISE-1545803

Title: Xylazine acts at excitatory presynaptic terminals of rat prefrontal cortex pyramidal neurons

Authors: J. QUIÑONES[1], J. ORTIZ[2], K. COLON[1], R. VAZQUEZ-TORRES[3], C. A. JIMENEZ-RIVERA[3], *P. SANABRIA-RAMIREZ[1]
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Abstract: The role of xylazine, a veterinary non-opiate sedative, in neuronal circuits associated with addiction is not well characterized. It has been recognized that this veterinary drug has been used as an adulterant in recreational drugs such as heroin and cocaine. Our previous in vitro electrophysiology studies have shown that 5 min perfusion of rat medial prefrontal (mPFC) cortex coronal slices with xylazine at 10 and 100 µM altered the firing pattern of layer V pyramidal cells. Here we examined whether xylazine modulates spontaneous excitatory synaptic transmission in mPFC. The preliminary data show that application of xylazine (100 µM) to whole cell patched mPFC pyramidal cells decreased the frequency (control 2.33 ± 0.55, xylazine 1.02 ± 0.55, n=4, p = 0.0124, paired t-test) of spontaneous excitatory postsynaptic currents

(sEPSCs) but not its amplitude (control, 25.01 ±1.36 pA, xylazine, 23.21 ± 2.12 pA, n =4, p=0.208, paired t-test). No changes were observed in either rise time (control, 1.76±0.30 ms, xylazine 1.67± 0.23 ms, n=4; p = 0.56) or decay time (control 3.70 ±1.20 ms, xylazine 2.58 ±0.54 ms, n=4; p = 0.28). These results are consistent with our previous observation that 100 µM xylazine significantly decreases mPFC pyramidal cell's firing (control- 8.45 ± 1.80 spikes, xylazine- 4.20 ± 1.128 spikes, n =5; p= 0.011, paired t-test). Pharmacologically, xylazine, is an alpha2-adrenergic agonist. Light and electron microscopy have shown that α2A-adrenergic receptors are distributed in axon terminals and somatodendritic processes in layer V of the mPFC. Therefore, these results suggest that xylazine might be acting at pre-synaptic terminals inhibiting glutamate release. We have also evaluated xylazine's effects in fast afterhyperpolarization potential (fAHP) since it has been shown that conductance responsible for fAHP contributes to firing properties of many cortical neurons. Xylazine, either at 10 or 100 µM had no effect on fAHP suggesting that its modulation of pyramidal cell activity is not mediated through the regulation of calcium activated voltage dependent potassium channels. These results constitute the first efforts to understand the effect of this drug of abuse adulterant at the level of the neuronal circuits involved in addiction.

Disclosures: J. Quiñones: None. **J. Ortiz:** None. **K. Colon:** None. **R. Vazquez-Torres:** None. **C.A. Jimenez-Rivera:** None. **P. Sanabria-Ramirez:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 691.01/JJ26

Topic: E.04. Voluntary Movements

Support: Cognitive Science Research Initiative, Department of Science and Technolog, India

Title: Differences in the structure of variability in movements of individual fingers and group of fingers

Authors: *V. SHANKAR, V. SKM
Indian Inst. of Technol., Chennai, India

Abstract: A task in biomechanics is usually produced by a system of elemental variables like variation in displacement of fingers, change in joint angles. While performing a simple task, the joint angles change and this leads to change in a required output variable.
Variance in a multidimensional space of elemental variables can be divided into two components. First one – [V_{UCM}] does not affect the performance variable and this lies within the Uncontrolled Manifold Space [*Scholz & Schöner, et al. 1999*]. Second component [V_{ORT}] lies in the orthogonal space and it affects the performance variable. Many studies have studied the

nature of these components of variance in multi-element tasks such as fingertip force production, aiming and pointing etc. In this study we attempt to document the changes in these components of variance in a kinematic learning task.
In our study, 10 right handed subjects (2 females) participated. Subjects viewed a template of a tube with a middle line and acceptable error ranges on the monitor. The Subjects were randomly divided into two groups – One Finger and Two Finger Group. One finger group practised with only *Index or Middle* finger and two finger group practised with *Index & Middle* fingers respectively. We mounted POLHEMUS - 2 micro + 1 standard sensors (2 on the tip of Index and Middle finger respectively + 1 Reference wrist sensor) to collect kinematic information. A customized LABVIEW Code was written for user interface and data was collected at 100 Hz. Subjects exerted maximum displacement of Index and Middle fingers separately, both in the flexion and extension directions. Subjects were required to move the fingers in such a way that the dot representing the vertical coordinate of their finger(s) moved over the tube as accurately as possible using either Index/Middle or both the fingers. Prior to practise all the groups had to perform similar Pre-test and Post-test using two fingers. Two performance scores, RMS(error) and Tout (total time outside the tube) were computed and provided as feedback to the subject. Both the groups showed a significant improvement in the performance indices with practise. Normalized good and bad variances (VUCM & VORT) were computed in the displacement space, averaged across subjects. Both the groups showed greater VUCM than VORT signifying stabilizing synergy. For the 2 finger group, a significant reduction in VUCM was observed with practise. But VORT decreased only for the one finger group but not for the two finger group. Our results are not consistent with similar experiments in kinetic domain. Further studies are needed to clarify the seemingly contradictory results from kinematics and kinetics of finger function.

Disclosures: **V. Shankar:** None. **V. Skm:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 691.02/JJ27

Topic: E.04. Voluntary Movements

Support: Cognitive science research initiative (CSRI),DST, India

Title: Dissociating improvements in speed and task performance in a novel motor sequence learning task

Authors: *D. R[1], R. RANGANATHAN[2], V. SKM[1]
[1]Applied Mechanics, Indian Inst. of Technology, Madras, Chennai, India; [2]Dept of Kinesiology, Michigan State Univ., East Lansing, MI

Abstract: The central phenomenon of motor learning is change in behavior in the course of time with practice. This improvement in behavior of a sequence learning task can be reflected as general improvements in speed and specific improvements related to sequence/keymap (task) being practiced. In our present study, we focused on segregating speed and keymap related components in a novel motor sequence learning task (glove based typing task) where we could manipulate the "keymap" – i.e the layout of the keyboard. 7 males and 1 female subject participated in the current study. Subjects typed words shown on the screen using a touch based glove that converted touches to ASCII code and sent it to computer via USB. Polhemus liberty standard sensors were used to collect the kinematic information of the thumb and wrist. Key press and key release time were collected in sync with the kinematic data at 100Hz in LAB VIEW. The temporal features such as completion time (time taken to complete a word correctly), dwell time (time stayed on an alphabet), errors in typing were calculated from the timing data. Movement time was computed from kinematic data. Key map (arrangement of alphabets on the glove) remained same for the first 6 days and from the 6th day subjects were asked to practice the keymap 2. Transfer blocks (T1 to T3) were tested during 1st, 3rd and 6th day of practice for key map 1 and 6th, 8th and 11th day of practice for key map 2. We observed that the performance of the variables improved with practice from day1 to day6 and once the key map was changed on day6 there was reduction in performance. However, we observed that performance in new keymap 2 was much better compared to day1 practice of key map 1. But this performance was not as good as day6 performance of key map 1. We performed one way repeated measures ANOVA for all the outcome variables with Transfer block as a factor (6 levels) and our results showed significant differences between T1 of the key map1 and T1 of key map2 ($P<0.05$) as well as between T3 of key map1 and T1 of key map2 ($P<0.05$). This suggests that there exists not only overall improvements in speed but also keymap-specific learning. We identified speed related learning as the improvement in performance between first practice of the two keymaps. Changing keymaps brings an interference in learning that is reflected in a reduction in performance from T3 transfer block to T1 transfer block. We hypothesize that this reduction in performance after changing the keymaps can be identified as key map related learning. Further studies can be performed to understand how exactly the variant and invariant features of a task can be used as a tool to enhance the motor performance in the kinematic domain.

Disclosures: **D. R:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Cognitive science research initiative (CSRI),DST, India. **R. Ranganathan:** None. **V. Skm:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Cognitive science research initiative (CSRI),DST, India.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 691.03/JJ28

Topic: E.04. Voluntary Movements

Support: Cognitive Science Research Initiative, Department of Science and Technology, India

Title: Interdependence of finger movements during flexion extension and neutral position of wrist

Authors: *N. C S, V. SKM
Indian Inst. of Technol. Madras, Chennai, India

Abstract: A task involving movement of one finger accompanies involuntary movement of neighbouring fingers of a human hand. This phenomenon is termed as Kinematic Enslavement(KE). KE is caused due to neural and mechanical connections of the fingers with muscles. Studies have shown that the movement of non instructed fingers is uniquely interdependent on the active instructed finger. When the wrist is flexed or extended, the tendons connecting the fingers are in tension or relaxation. In this study, we investigated the changes in finger interdependence, over various hand postures. 4 male and 2 female subjects, with no neuro-muscular disorders, participated in this experiment. The task was to perform cyclic flexion-extension of Index, middle, ring and little fingers one at a time for three different wrist positions - flexion 30^0, neutral 0^0 and extension 30^0. The kinematic data of all the phalanges of these four fingers were collected using 16 sensor Polhemus Liberty data acquisition system, at 100Hz, with the help of a LabVIEW GUI. The first part of the task involved measurement of the maximum flexion - extension of each finger, at three different postures. The second part involved 3 trials of cyclic flexion - extension for 30s each, in synchronous to a 1.5Hz metronome beep (movement of 0.75Hz) within the range of 65% - 85% of the maximum. Subjects were occasionally instructed to concentrate on only the active finger and ignore any movement of the non instructed fingers. Individual movement cycles were filtered at 5Hz and segregated based on the amplitude and frequency matching. Enslavement matrix was computed by averaging the slopes between finger position data, for three different hand postures. Individuation Index (II) was derived for the three different postures and was compared. Statistical analysis showed that there was a consistent drop in Individuation Index of the middle finger in the case of flexion and extension of the wrist as compared to the neutral case. And also, the decrease of Individuation Index in the flexion case was more than that of extension. Changes in Individuation Index were observed for the other fingers but were subject specific.

Disclosures: N. C s: None. **V. Skm:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 691.04/JJ29

Topic: E.04. Voluntary Movements

Title: A behavioural model for a visuomotor adaptation task using index and little finger forces

Authors: *S. SALAM[1], S. VARADHAN[2]
[1]Indian Inst. of Technol., Chennai, India; [2]Indian Inst. of Technol. Madras, Chennai, India

Abstract: Background:
To our knowledge, the 'models' available in kinematics space such as reaching, or grasping isn't as limited as what is understood for the kinetics space. While further explicitly designed experiments are inevitable, we used a dataset that was earlier obtained from a study on effects of various sensory modalities on motor performance. System identification techniques were used to study the underlying motor control mechanism that leads to the observed structure of motor variability.
Methods:
12 healthy right handed subjects (6 males; age: 25.25 ± 3.05 years) participated in the study. A cursor on the visual feedback screen was controlled by the index and little finger forces (along horizontal and vertical axes respectively) using two force sensors (Nano-17, ATI) sampled at 200 Hz through an environment designed in LabVIEW. After sufficient training to 'move properly' in the perceived space for the novel visuomotor task, the subjects were instructed to "reach the target about any of the ideal path" accurately. The subjects performed 15 trials each for 4 experimental blocks for 4 mechanical effort biasing (MEB) ratio of 1:1 (15 - 15), 1.5:1 (15 - 10), 2:1 (15 - 7.5) and 3:1 (15 - 5) (as percentage of maximum voluntary contraction force of index (I) and little (L) finger force respectively).
Correlation (auto/cross) function were computed for the task parameters of a trial: the I and L finger forces, and their rate of change, the joint vector and its rate of change, and the deviation*. Effects across blocks (of MEB ratio) were checked on performance indexes of a trial performance which include precision* in both visual and force space, correction ratio* and completion time. (*Specific methods not included here.)
Results and discussion:
Within a trial, the performance variables is affected by decreasing weights of its most recent performance. The weights for different task parameters decay at different rates reflecting their corresponding relevance (or irrelevance) in successfully executing such a goal oriented task. Across trials, even though the degree of control (formally the correction/adaptation factor) varies as an individual's ability, the ACF coefficients for small lags were consistently ordered. The small coefficients that decays sharply implies minimal learning effects across trials.

In sum, such similar features of planning as well as execution in both kinetics and kinematics reflects the behavioural property of the human control system which follows the same hierarchy of constraints, regardless of the observation (or performance) space.

Disclosures: S. Salam: None. **S. Varadhan:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 691.05/JJ30

Topic: E.04. Voluntary Movements

Support: New Faculty Seed Grant, IITM

Title: Hand dominance and grip force variability in a dynamic bimanual manipulation task

Authors: *R. BANUVATHY, S. ANNAMALAI, V. SKM
Indian Inst. of Technology, Madras, Chennai, India

Abstract: In everyday life, most of the activities demand the use of both hands to perform a task. Proper coordination of fingertip forces of both hands is essential for the better performance of a bimanual task. According to dynamic dominance hypothesis (Sainburg RL, 2002), dominant hand is effective and consistent for performing dynamic tasks and the non-dominant hand for static tasks, in kinematic space. The objective of this experiment is to understand the role of hand dominance in kinetic space while performing a dynamic bimanual task. We hypothesized that the variability in the grip force of the right hand when it is involved in cyclic movement is lesser when compared to the variability in grip force when left hand is moving. Our experiment involved a dynamic bimanual manipulation task. The task involves lifting a manipulandum having two handles of height 25cm separated by acrylic hollow tube of length 40cm fitted with two Polhemus standard position sensors and four, 6 axis ATI Nano 17 force sensors on either handles. This customized manipulandum was utilized to record grip and load forces produced by the index finger and thumb of the two hands of the participants. Five male and four female subjects were instructed to lift the handles with both the hands to a height of 5cm above the table through precision pinch grip with their upper arm positioned vertically and elbow flexed 90° and then they were asked to make cyclic up and down movements with the instructed hand. The subjects were provided with visual feedback of instructed hand through its position data on the monitor and requested to time their movements in such a way that they are either at peak or trough during the metronome beep (1.33Hz) which acted as a cue for speed. Force and position data were sampled at 100Hz and collected while the participants performing the task. Difference in variance of right hand thumb and index fingertip grip forces is lesser than the left hand thumb and index fingertip grip forces both during the moving and static state. From the preliminary

analysis of the data, we were able to understand that the dominant hand shows lesser variation in grip force for both dynamic and static task in kinetic space. Further study of the tangential forces and coordination between tangential and grip forces can help us corroborate the results with the results in kinematics domain on dynamic dominance.

Disclosures: R. Banuvathy: None. **S. Annamalai:** None. **V. Skm:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 691.06/KK1

Topic: E.04. Voluntary Movements

Support: FWO Odysseus (Belgium)

BBSRC David Phillips fellowship (UK)

Title: Force planning depends on experiencing object weight during lift but not holding

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Abstract: Skilled object manipulation requires the planning of a motor command appropriate to the object properties. For instance, to lift an object, fingertip forces must be scaled according to object weight. To ensure a smooth lifting motion, the brain plans these forces before lift onset and, if necessary, adjusts the force output based on rapid sensory feedback loops during the lifting phase. When lifting a series of different objects, the planning of fingertip forces are influenced by the weight of the previous object, an effect often referred to as sensorimotor memory. In this study, we investigated whether force planning is based on a sensorimotor memory of the previous object weight that can be experienced either during the dynamic lifting phase or during the static holding phase. We used a virtual reality environment to manipulate object weight after lifting had commenced. Participants (N=9) lifted a semi-randomized series of objects that could decrease or increase in weight during the holding phase. For instance, a light object lift could be followed by a heavy object holding or, conversely, a heavy object lift could be followed by a light object holding. We analysed the effect of object weight changes on fingertip force rates applied on the next object lift as a way to quantify motor planning and compared them to control trials in which object weight was not altered. This allowed us to test whether sensorimotor memories used for force planning rely more on the dynamic lifting phase or the static holding phase. We found that force planning was based on the previous object weight experienced during the lifting phase ($p=0.009$), but not during the holding phase

(p=0.37). This indicates that sensorimotor memory is generated by collecting information about weight over a transient period. We suggest the lifting phase is a key time period for mediating sensorimotor memory. The comparison between expected and actual sensory inputs that take place within this time period could be more critical than information acquired during static holding for building up an object representation that can be used for the planning of future interactions with objects.

Disclosures: V. Van Polanen: None. **M. Davare:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 691.07/KK2

Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI Grant Number JP15H01671

Title: Differences in alpha and beta ERD patterns during various grasping movements

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Abstract: The hands are primary interface for us to interact with the world. The hand motions to interact with objects can be roughly divided into reaching and grasping. To identify neurophysiological representation of these motions is important to construct brain-machine interface system which, for example, can control prosthetic hands. Event related desynchronizations (ERDs) in alpha (8-12Hz) and beta (18-24Hz) band in electroencepharogram (EEG) are the common phenomena that reflect sensorimotor brain activity. We investigated the difference in ERD patterns during various grasping movements. One right-handed subject (male, aged 24) was participated in our experiment. The subject was instructed to reach and grasp 6 daily-use objects at his own timing. These objects corresponded 6 grasping forms according to Kamakura's classification of human grasping. Each form can be categorized into 3 classes : power grip (Pwr), intermediate grip (Itm) and precision grip (Prc). EEG signals were sampled at 1200Hz from 30ch electrodes selected from the extended international 10/20 system, and major finger joints were sampled at 64Hz from 18ch bend sensor by using a data glove. The subject usually performed reaching and grasping movements within 2.5 s. The reaching movement peaked at around 1s after the task onset, the subject grasped and held the object for 1.5 s. The intertrial interval was 1s. For ERD analysis, EEG data were transformed into time-frequency data by using Wavelet transform and standardized by the mean power between -1 to -0.5 s before the task onset. We applied t-test ($p < 0.5$) to alpha and beta bands of the EEG data which was segmented into 250 ms time bins sliding by 50 ms with overlap. The result showed that there

were significant ERDs at C3, but the alpha and beta ERD patterns were different among grasping forms. Around the task onset (-0.2 to 0.4 s), alpha and beta ERDs were commonly observed in all movements. In holding duration (1 to 1.5s), beta ERD was commonly disappeared. However ERD were intermittently observed in Pwr and Prc movements, but not in Itm. After holding duration (1.5 to 2.5 s), alpha and beta ERDs were similarly observed in Itm and Prc, but not in Pwr. These result suggest that ERD patterns in the motor cortex during grasping movements are different depending on its grasping forms.

Disclosures: Y. Inamura: None. **S. Shimada:** None.

Poster

691. The Control of Grasp and Grip I

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Topic: E.04. Voluntary Movements

Support: fonds wetenschappelijk onderzoek (fwo) belgium

Title: Effects of observing correct or incorrect motor plans on predictive force control during object lifting

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Abstract: Recent studies have established that, when two individuals have to lift the same object sequentially, observation of lifting errors mediates perceptual weight judgement and enables the observer to update his internal object representation without actual sensorimotor experience. For example, observing an actor overestimate the force needed to lift an object allows the observer to subsequently downscale his fingertip forces to lift the object in a single and smooth motion. However, it is still unknown whether the observation of an accurately planned lift is also able to update these internal sensorimotor representations. Here, we tested this hypothesis by asking participants to perform a dyadic interaction task. Thirteen healthy volunteers were recruited to grasp and lift a manipulandum in alternation with an actor. Every 3rd to 6th trial performed by the actor the object weight changed unpredictably between either 2 or 6N. Participants were informed that (1) they would always lift the same weight as the actor did in the preceding trial and, (2) based on the task condition, the actor would perform either a skilful lift (accurately estimating object weight) or lifting errors (over- or underestimating object weight). Subjects were always required to lift objects as accurately as possible. First, when visuomotor cues were absent (task performed without actor), subjects made typical force overestimation or underestimation errors (both $p<0.001$) when object weight unpredictably switched from heavy to

light or light to heavy, respectively. Second, and in line with current literature, when observing the actor making these typical lifting force errors, subjects could accurately plan their fingertip forces according to the actual object weight (both $p<0.001$). Third, our results show that participants were also able to predict the actual object weight after observing accurately planned lifts but only for heavy ($p<0.001$) and not light objects (ns.). This highlights that predictive scaling of lifting forces is strongly mediated by observing sensorimotor errors but can also be driven by more subtle differences in observed visuomotor information. Altogether our results add to the current knowledge about the relative contribution of different visuomotor cues to predicting object weight for the control of skilled hand-object interactions.

Disclosures: G. Rens: None. **M. Davare:** None.

Poster

691. The Control of Grasp and Grip I

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Topic: E.04. Voluntary Movements

Support: NIH Grant NS095873

Title: Force illusions caused by muscle vibration

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Abstract: We used the hypothesis that the neural control of movement can be adequately described as the specifications of time patterns for spatial referent coordinates (RCs) of the effector, and that abundant afferent signals report on deviations of the effector from its RC. Within this hypothesis, perceptions of force and position are interrelated, so muscle vibration is expected to cause illusions of both position of and force produced by an effector. Vibration-induced position illusions have been well documented, but force illusions have not been reported; observing such illusions was the main goal of the study. To explore the generality of such illusions, we studied force matching by both dominant and non-dominant hand during accurate force production under visual feedback and also during unintentional force drifts caused by turning the visual feedback off. Subjects pressed with all four fingers of either hand on individual force sensors and used visual feedback to produce accurate steady force level with one hand. When visual feedback was turned off, the subjects were asked to continue producing the same force and to match the perceived force by pressing for a few seconds with the other hand. Vibration at 80 Hz was applied to extensor muscles in either or both forearms. Turning visual feedback off led to a slow decrease in force production. Vibration of the extensors reduced the

magnitude of the force drift. There was no time drift in the matching hand performance even as the force produced by the other hand decreased. Vibrating the forearm involved in the continuous task led to higher matching hand forces, while vibrating the forearm that performed the matching task led to lower matching hand forces. These effects suggest that force produced by the hand under vibration was consistently overestimated by the central nervous system. Taken together, our observations suggest that muscle vibration leads to changes not only in the sensory component of kinesthetic perception but also in the RC component: vibration of the extensors effectively pushed RC values into the direction of flexion. These observations support the scheme for kinesthetic perception based on the RC concept. They suggest that the force drift originates not at a hierarchically high task level (e.g., as a result of a drift in working memory), but at an intermediate level which is responsible for interactions between the hypothetical control variables (time-varying RCs) and feedback signals on current effector configuration.

Disclosures: C. Cuadra: None. **S. Reschechtko:** None. **M.L. Latash:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

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Program#/Poster#: 691.10/KK5

Topic: E.04. Voluntary Movements

Support: Schaefer School of Engineering & Science at Stevens Institute of Technology

Title: Cognitive agency in hand grasp performance - implications for rehabilitation

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Abstract: Improving hand grasp function impaired by neuromuscular pathology is a critical objective in rehabilitating performance of activities of daily living. Standard rehabilitation protocols rely on the repetitive practice of grasp to better learn operation of an assistive device or re-formulate neuromotor connections. Virtual reality (VR) environments that heighten patient engagement have been utilized to accelerate training progress. But adapting a person's cognitive perception of the training to improve functional performance has not been thoroughly examined. Our objective is to develop a VR platform that investigates the role of cognitive agency in hand grasp performance. We hypothesize that improved grasp performance will be achieved with a greater sense of *agency*, the perception of being the "true author" of one's hand movements. Our methodology aims to systematically vary a subject's perception of agency over a computer hand and to observe the correlation with performance of grasp force and motion tasks. Demonstrating how individuals perform with greater agency will potentially provide a powerful basis for creating rehabilitation protocols that are more intuitive and more efficient. If the functional

connection between agency and performance is established, agency can be a highly viable criterion to optimize rehabilitation protocols that rely on repetitive task execution. Across repetitions, operational parameters of assistive devices or therapies such as non-invasive brain stimulation may be better adapted with the expressed purpose of maximizing agency-dependent performance. Such a test-bed can then be extended as a concept platform for more efficient movement rehabilitation following neuromuscular pathologies such as spinal cord injury, stroke, or upper-limb amputation. Related findings may facilitate more optimal parameters for controllers, generate greater motor gains with fewer practice repetitions, and better incorporate the user in device operation. Foundational methods could be employed towards improved development of exoskeletons, approaches using functional electrical stimulation, and sensory-feedback prostheses.

Disclosures: R. Nataraj: None.

Poster

691. The Control of Grasp and Grip I

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Topic: E.04. Voluntary Movements

Support: NIH Grant NS035032

NIH Grant NS095873

Title: Hierarchical organization of force and moment stabilizing synergies in the space of theoretical control variables

Authors: *S. RESCHECHTKO, M. L. LATASH
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Abstract: We used the theory of control with referent coordinates (RCs; Feldman 2015) and the framework of the uncontrolled manifold (UCM) hypothesis (Scholz and Schöner 1999) to study force- and moment-stabilizing synergies in the space of hypothetical control variables. These theoretical control variables were associated with referent coordinate (RC) and apparent stiffness (k) of the effector. We analyzed inter-trial co-variation of those variables during isometric multi-finger pressing tasks and drifts in such co-variation after visual feedback was turned off. Subjects performed isometric pressing tasks with the four fingers of the dominant hand during which they produced a precise combination of total force and supination moment. For the first 8 s of each trial, subjects received visual feedback on total force and moment. After the first 8 s, one of the following feedback schemes was imposed for the remaining 13 s of the trial: (1) no feedback was displayed; (2) only force feedback was displayed; (3) only moment feedback was displayed. RC

and k of each finger were recorded twice per trial by changing the location (AC) of all four fingertips using the “inverse piano” device (Martin et al. 2011) and measuring the resultant changes in force production (cf. Ambike et al. 2016). RC and k were recorded once during visual feedback (5 s after trial initiation) and once close to the end of the trial after visual feedback was manipulated. When feedback was removed, subjects displayed drifts in the variable(s) with missing feedback. Without feedback, total force decreased and total moment drifted into pronation values. UCM-based analysis of finger force variance showed that synergies stabilizing total force or total moment of force were strong under visual feedback but disappeared over the course of drifts in performance. Pairs of RC and k measured in different trials were matched via random permutation and the force values computed from these pairs yielded much more variable total force and moment than was observed in experimental conditions, even after performance drifts. The difference between inter-trial variability in force produced by permuted and actual {RC k} pairs was smaller, however, after such performance drifts. These results indicate that the CNS stabilizes performance by organizing synergies in the {RC k} space at the hand level as well as at the individual finger level. This stabilization is most effective under visual feedback, but it persists at the level of control variables even without visual feedback.

Disclosures: S. Reschechtko: None. **M.L. Latash:** None.

Poster

691. The Control of Grasp and Grip I

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Topic: E.04. Voluntary Movements

Title: Complexity of movements in humans with 6 fingered hands

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Abstract: Brains control body parts with many degrees of freedom (d.o.f.) to produce complex movements. How brains control multiple d.o.f. and can make use of the complexity of the effector space for movement is barely understood. Here we address the following questions:If the number of d.o.f. of the effector increases, can the human motor system use this additional complexity for purposeful movements? Or will the complexity of movement be limited due to

finite neural resources or limited complexity of neuronal computations?
As a case study to address this question, we compared the complexity of movement between 13 normal five-fingered subjects and 2 subjects with six-fingered hands, who had fully functional supernumerary fingers between thumb and index finger on both hands and fully functional regular fingers. Electromagnetic motion-capture sensors (12 and 14 for five and six fingered) were attached to their right hand and captured the hand movements during haptic exploration tasks and different real-world task (tying shoe laces, flipping book pages, origami and rolling a towel). In the haptic exploration task subjects were blindfolded and they were asked to explore one of 50 objects with diverse size and shape, to guess what it was.
Principal component analysis was performed and the number of components to explain 90% of the variance in the data was calculated. This value can be considered as an estimate of the effective d.o.f of the movements. Six-fingered hands required a significantly higher number of components (12 and 12 from 39 dimension of captured data), compared to five fingered subjects (8.4~10.5 from 33 dimensions 95% confidence interval).
We discretized the finger movements into 243 ($=3^5$, five fingered subjects) or 729($=3^6$, six fingered subjects) different action states where the movement of each finger was classified as either folding, unfolding or not moving. This enabled us to analyze the complexity of movements using information entropy. The joint entropy of six fingers (8.52 and 8.26 bits) was significantly larger than that of five fingered subjects (6.84±0.04 bits). Interestingly, the joint entropies were only 9.3%, 11.8% and 11.3% smaller than the sum of the independent entropy of the fingers (9.39, 9.36 and 7.71±0.02 bits).
Our results suggest that six-fingered individuals can produce more complex hand movements with more effective d.o.f. than five fingered individuals. This supports the idea that the human motor system can exploit the additional d.o.f. of six-fingered hands to increase the complexity of hand movements.

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Poster

691. The Control of Grasp and Grip I

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Topic: E.04. Voluntary Movements

Support: ESA (European Space Agency)

IAP VII/19 DYSCO (BELSPO, Belgian Federal Government)

Title: Partial-gravity as an extended insight on the adaptive and learning mechanisms of the CNS during rhythmic arm movements

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Abstract: Several studies have investigated the kinematics and dynamics of precision grip during cyclic movements of the arm in normal (1 g), micro- (0 g) and hyper- (1.8 g) gravity fields. These studies have highlighted the ability of the central nervous system (CNS) to adapt its internal predictive models to new environments (Augurelle et al., 2003; White et al., 2005) and the ability of subcortical central pattern generators (CPGs) to adapt the frequency of rhythmic movements to a new gravitational context (White et al., 2008). The objective of the present study was to extend these results by investigating the same movements when performed in partial-gravity environments during two partial-g parabolic flight campaigns. Fourteen subjects participated in the experiment. Six subjects were experienced with respect to exposure to micro-gravity whereas eight were not. Participants performed vertical oscillations of the extended arm with a manipulandum held in precision grip while being exposed to five different gravitational conditions: normal (1 g), micro- (0 g), Lunar (0.16 g), Martian (0.38 g) and hyper- (1.8 g) gravity. Two LEDs constrained the amplitude of the movements and the subjects chose the frequency that they considered most comfortable. Results showed that for most subjects, movement frequency increased as the gravity level increased, but that microgravity was a singular point, supporting previous results (White et al., 2008). For most of the subjects, the frequency remained stable within conditions from the first trials, suggesting that a low-level mechanism such as a subcortical CPG drives the movement frequency. We also investigated the evolution of the grip force (GF) according to the load force (LF) variations within each parabola and across parabolas. The analysis of the dynamics thereby provides a more comprehensive insight on the adaptive and learning mechanisms of the CNS when exposed to completely novel environment dynamics.

Disclosures: L. Opsomer: None. **V. Théate:** None. **P. Lefevre:** None. **J. Thonnard:** None.

Poster

691. The Control of Grasp and Grip I

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Topic: E.04. Voluntary Movements

Title: Effects of a cognitive task on the grip force control in two manipulative tasks

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Abstract: In many everyday situations, we hold and/or carry an object while performing other motor or cognitive activities. The magnitude of grip force (GF), responsible for avoiding object slippage caused by a load force (LF), increased during simultaneous execution of a cognitive and a lifting and holding task. However, it is unknown whether there is influence of the cognitive task in GF and LF control and coordination during a cyclical manipulation task, with a higher level of automatization. To evaluate whether the execution of a cognitive task influences the GF and LF control and coordination during the execution of manipulation tasks involving sequential or cyclic movements. Fifteen right-handed, young and healthy adults performed two motor tasks consisting of i) grasping, lifting, and holding a 214 g instrumented object for 15 seconds; and ii) holding the object and moving it up and down continuously for about 20 centimeters at their preferred frequencies for 15 seconds. The tasks were performed in isolation or simultaneously to a cognitive task (dual task). The cognitive task was performed in isolation to verify whether performing a motor task simultaneously affects the performance on the cognitive task. The cognitive task was to recall the number of images of houses (5 per trial) in which either a ladder and garage, or a ladder and a car could be identified and to report the response verbally at the end of each trial. The results revealed that during the dual task the peak of GF during lifting and the averaged GF during holding were greater than when only the motor task was performed. Individuals were more conservative by increasing the GF magnitude in a predictive way when performing the sequential motor task simultaneously to a cognitive task. The results also revealed that the coefficient of cross-correlation between GF and LF was higher during the dual task condition in a cyclical manipulation task. Also, the errors in the cognitive task were higher when it was associated with the sequential manipulation task, but not during the cyclical manipulation task. These findings indicate that the cyclical manipulation task, unlike the sequential task, does not require attentional resources for its performance.

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Poster

691. The Control of Grasp and Grip I

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Topic: E.04. Voluntary Movements

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FIRB 2013,RBFR132BKP

Fondazione del Monte di Bologna e Ravenna, Italy

Title: Differential preparatory activity for reaching and grasping movements in area V6A of the macaque monkey

Authors: *P. FATTORI, E. SANTANDREA, R. BREVEGLIERI, A. BOSCO, C. GALLETTI
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Abstract: Over the years, electrophysiological recordings in macaque monkeys performing visuomotor tasks brought about accumulating evidence for the expression of several neuronal properties in the posterior parietal area V6A, including selectivity in the visuospatial and somatosensory domains, and encoding of visual affordances and motor cues. Altogether, these properties build an ideal neural substrate for allowing control of prehension. Moreover, pre-movement population activity in monkey V6A has been recently shown to convey grip-related information for upcoming grasping actions. Here we directly tested whether macaque V6A neurons encode preparatory signals specifically related to the arm/hand action to be performed, thus differentiating between dissimilar actions before movement onset. The activity of 85 V6A neurons was recorded from 2 monkeys (*Macaca fascicularis*) during the execution of two visuomotor tasks sharing the same spatio-temporal structure, in which the animals were instructed to perform either reaching or grasping movements. To control for any influence of visual information on pre-movement activity, tasks were carried out both in darkness and in light. In most V6A neurons, a selective task-related activity was expressed in anticipation of action execution, effectively differentiating between arm/hand movements aimed at reaching a specific location and arm/hand movements aimed at grasping a handle at the exact same location with appropriate wrist orientation and grip execution. Such action-specific pre-movement activity was expressed in more than half of V6A neurons in our dataset, either alone (*Task cells*, 26/85, 31%) or in combination with sensitivity for visual feedback (*Task/Background cells*, 21/85, 25%). Stronger pre-movement activity was observed more often in the grasping vs. reaching task (*Task cells*: 69% vs. 31%; *Task/Background cells*: 67% vs. 33%). Most importantly, we found striking consistency in neural discharges measured during pre-movement and movement epochs, suggesting that the former is a preparatory activity implementing suitable motor programs which support subsequent action execution. In sum, our findings support a role of V6A in planning and execution of prehensile actions (notably grasping), and strengthen the emerging view that areas in the dorsomedial and dorsolateral visual stream act as cooperating routes for controlling the whole act of prehension.

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Poster

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LSM – CAPES PhD Scholarship

Title: Enhancement of force steadiness induced by synusoidal vibrotactile stimulation depends on contraction intensity

Authors: *C. M. GERMER, L. S. MOREIRA, L. A. ELIAS
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Abstract: Motor control studies have shown that an optimal level of additive noise on cutaneous mechanoreceptors improves motor performance and electrophysiological recordings in humans. The phenomenon behind these improvements seems to be the so-called stochastic resonance. As far as we know, the effects of contraction intensity on the improvement of force control induced by vibrotactile stimulation was not yet explored. The aim was to evaluate whether supra-threshold sinusoidal vibration applied to the skin improves motor performance during a force control task. Additionally, we aimed at investigating if contraction intensity affects this enhancement. Healthy young subjects (N=6, 4 males, 29±4 yr) performed a visually guided force-matching task, which consisted of an abduction of the non-dominant index finger. A mechanical vibration was delivered by a linear resonant actuator (f=175Hz) positioned at the proximal phalanx of the index finger. Subjects were asked to perform isometric contractions with the first dorsal interosseous muscle at three target levels: 5%, 10% and 15% of maximal voluntary contraction (MVC). Five trials of 30s were performed at each contraction intensity. In order to evaluate the effects of mechanical vibration, a random sequence of five supra-threshold stimuli (amplitude 0.05G to 1.5G) was applied at each trial and a control condition (i.e. no vibration, Ctrl) was also considered. Each vibration intensity lasted 4s. Force variability and precision were assessed by the coefficient of variation (CV) and root mean squared error from the target (RMSE), respectively. The vibration level at which the best performance was achieved was considered as the optimal stimulation (OS). The force CV decreased from 0.030±0.005 at 5%MVC to 0.018±0.002 ($p=0.0001$) and 0.019±0.003 ($p=0.0004$) at 10% and 15%MVC, respectively. Similarly, the RMSE was significantly smaller in 5%MVC (0.0022±0.0004) as compared with 10%MVC (0.0030±0.0003, $p=0.014$) and 15%MVC (0.0038±0.0004, $p<0.0001$). There was a significant difference between Ctrl and OS for the CV (0.025±0.005 vs.

0.020±0.003, p=0.01) as well as for the RMSE (0.0033±0.0005 vs. 0.0027±0.0004, p=0.02). At 5%MVC OS enhanced force CV by 29±10%, which was significantly higher than at 10%MVC (8±8%, p=0.02) but not than at 15%MVC (17±11%, p=0.2). However, albeit OS improved RMSE by ~15%, there was no statistical difference among the contraction intensities. These results suggest that supra-threshold sinusoidal vibrotactile stimulation with an appropriate level (different from zero) improves isometric force control, but the enhancement is higher during low-intensity contractions.

Disclosures: C.M. Germer: None. **L.S. Moreira:** None. **L.A. Elias:** None.

Poster

691. The Control of Grasp and Grip I

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Title: Spatiotemporal profiles of neuromagnetic oscillatory changes related to the movement imitation

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Abstract: Imitation is a higher-order processing of cognitive and motor functions organized by the central nervous system. This process requires an observation-execution matching system that transforms an observed action into an identical movement performed by the observer. Recent studies have demonstrated the involvement of oscillatory neural activities during imitation in low-frequency components such as the alpha and beta bands. Although the low-gamma band is thought to reflect higher cognitive processes, no studies have focused on it. In the present study, we used magnetoencephalography (MEG) to examine the frequency-dependent neural oscillatory changes not only in the alpha and beta bands but also in the low-gamma band during imitation. Twelve healthy, right-handed participants performed a finger task consisting of 4 conditions

(imitation, execution, observation, and rest). Under imitation and execution conditions, significant attenuations of oscillatory power [termed as event-related desynchronizations (ERDs)] were observed at the left frontal, central, and parietal MEG sensors in the alpha, beta, and low-gamma bands. Functional connectivity analysis using imaginary coherence exhibited an imitation-specific network in the front-central regions in the low-gamma band. Furthermore, synthetic aperture magnetometry (SAM) analysis showed significant ERDs in the low-gamma band at the left sensorimotor area and middle frontal gyrus (MFG) during the imitation condition as compared with those in other conditions. Our results suggest that the oscillatory neural activities of the low-gamma band at the sensorimotor area and MFG play an important role in the observation-execution matching system related to imitation.

Disclosures: H. Sugata: None. **M. Hirata:** None. **Y. Tamura:** None. **T. Araki:** None. **H. Onishi:** None. **S. Yorifuji:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 691.18/KK13

Topic: E.04. Voluntary Movements

Support: NSERC

Title: Perceptual and visuomotor tasks respectively adhere to and violate Weber's law in response to functionally graspable target objects

Authors: *J. MANZONE[1], M. PECORA[1], M. KHAN[1], S. DAVARPANAH JAZI[2,4], M. HEATH[1,3]
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Abstract: Within-participant variability of peak grip aperture provides a measure of just-noticeable-difference (JND) values that are used to address whether responses adhere to or violate the relative psychophysical properties of Weber's law. Evidence from our group indicate that open-loop grasping and perceptual size estimates (i.e., manual estimation) respectively violate and adhere to Weber's law - an indication of visual processing mediated via the dorsal and ventral visual stream. However, recent work has questioned the utility of Weber's law in concluding the neural correlates of actions when responding to objects that approach the biomechanical limits of our grip aperture. Specifically, Bruno et al. (2016: Neuropsychologia) reported that both visuomotor (i.e., open loop grasping) and perception based tasks (i.e., manual estimations) adhere to Weber's law at 'small' (5-20mm width), but violate the law at 'large' objects (40-120mm width) with the latter finding being attributing to the reduced biomechanical

freedom associated with aperture opening. It is important to note that the larger objects used may have exceeded the functionally graspable range of participants' grip aperture leading to artificial constraints on the associated JND values. Thus, in the present investigation participants performed a visuomotor (i.e., open-loop grasping) and two perceptual size estimation tasks on objects with widths that matched decile increments (i.e., 10-80%) of their specific maximal aperture separation. The open-loop grasping task required participants to reach-to-grasp objects while the perceptual size estimates required participants to match the long-axis of an object by either separating the distance between their thumb and forefinger (i.e., manual estimation task) or by adjusting the width of a computer-generated object on a screen (i.e., method of adjustment task). All tasks were completed without vision of the target object (i.e., in visual open loop conditions). Results showed that the visuomotor task produced a null scaling of JNDs to object size (i.e., violation of Weber's law) and perceptual size estimates produced JND/object size scaling (i.e., adherence to Weber's law) - a set of results incompatible with the biomechanical constraint hypothesis. Alternatively, our findings support the utility of Weber's law through the entire functional range of grip aperture separation and demonstrate absolute and relative processing of visuomotor and perceptual tasks, respectively.

Disclosures: **J. Manzone:** None. **M. Pecora:** None. **M. Khan:** None. **S. Davarpanah Jazi:** None. **M. Heath:** None.

Poster

691. The Control of Grasp and Grip I

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Program#/Poster#: 691.19/KK14

Topic: E.04. Voluntary Movements

Support: NIH Grant UL1 TR002014

NIH Grant KL2 TR002015

Social Science Research Institute, The Pennsylvania State University

Title: Self-reported sensory perception is related to precision grip force in healthy young adults

Authors: *J. TUCKER[1], A. MERIDA[1], C. R. DAHM[2], A. J. GROFF[2], P. WANG[2], N. M. ETTER[3], K. A. NEELY[2]
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Abstract: Understanding the perception-action relationship is particularly relevant for the study of neurodevelopmental disorders. Our recent work reports subtle differences in grip force output in adults with and without ADHD (Neely et al., 2016, 2017). However, it is unknown whether

somatosensory deficits contributed to these differences. Thus, we sought to determine the relationship between grip force, tactile threshold estimates, and a trait measure of sensory processing in healthy young adults (N=20). In the motor task, participants produced force for 4 s separated by 2 s of rest, for a total of 5 trials in one 30-second block. Blocks were repeated 4 times and separated by 12 s of rest, for a total of 20 trials. Participants completed 7 target conditions from 5% to 50% of their maximum voluntary contraction. In the somatosensory task, tactile detection and discrimination threshold estimates were obtained for the right index finger, thumb, and hypothenar muscle region of the palm. Participants completed the Adolescent/Adult Sensory Profile (AASP), a trait measure of sensory processing comprised of self-report items related to everyday sensory experiences. The AASP is divided into four subscales based on Dunn's Model of Sensory Processing (1997): low registration, sensation seeking, sensory sensitivity, and sensation avoiding. We hypothesized force output would be related to somatosensory measures, but not AASP. To test this hypothesis, we conducted bivariate correlations between force output, tactile threshold estimates, and quadrant scores on the AASP. Force output variables included root mean square error, coefficient of variation, and rate of change from baseline to the target (rate-on) and from target to baseline (rate-off). Counter to our hypothesis, force output was not consistently correlated with somatosensory assessments, but was correlated with the AASP. Rate-on was correlated with sensation seeking, such that individuals with high sensation seeking scores were slower to reach the target on 5 of 7 conditions. Sensation seeking reflects characteristics such as the pursuit of sensory stimuli. Rate-off was correlated with low registration, such that individuals with low sensory registration scores elicited slower rates of change on all 7 conditions. Low registration scores relate to behaviors such as missing or responding slowly to stimuli. Our findings suggest these clinical somatosensory measures may not be sensitive enough to detect subtle differences in healthy young adults. High-precision methods are needed to identify subclinical traits associated with tactile feedback and grip force production in healthy young adults.

Disclosures: J. Tucker: None. **A. Merida:** None. **C.R. Dahm:** None. **A.J. Groff:** None. **P. Wang:** None. **N.M. Etter:** None. **K.A. Neely:** None.

Poster

691. The Control of Grasp and Grip I

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Program#/Poster#: 691.20/KK15

Topic: E.04. Voluntary Movements

Title: Is learning encoded in the resting brain?

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Abstract: Why do some people acquire a novel motor skill with relative ease and efficiency, while others struggle and eventually fail? There are reports of individuals who are unable to learn even after extensive practice (Brooks et al. 1995). Our long-term goal is to discover a simple, accurate and reliable brain biomarker of motor learning capability; this would promote development of personalized training programs to foster motor learning in athletic and rehabilitation settings. Our primary aim in this study is to determine if resting-state electroencephalography (rs-EEG) can be used to predict motor learning capability in non-disabled individuals. **Methods:** Nineteen non-disabled adults (8 females, mean age 25.7 +/- 2.8 yrs) participated. We used a discovery learning task to discriminate if participants can discover the movement strategy that governed task success. We adapted the Brooks' (1995) task--the objective is to use a thumb joystick to move a cursor from a start box to a stop box in $\leq$ 3 sec. Unknown to the participants, the coupling of joystick to cursor movement is determined through rate control, not typical position control. This required participants to search the environment for the right movement pattern. We measured their level of search by calculating the variance of the cursor movement during early performance. Participants practiced 200 trials of the task on Day 1 of the experiment and 50 retention trials on Day 2 (24 hours later). Prior to practice on Day 1, 5 min of rs-EEG were acquired using a 64 lead EEG cap. We used a support vector machine to determine which intercortical connectivity measures-previously recorded during pre-practice rs-EEG--were most predictive of early search. **Results:** Participants had a wide range of performance capabilities with some individuals capable of many successful trials and others with few to zero. However, the amount of search during early practice predicted the accuracy with which each participant could execute the task rule during late performance on Day 1 and retention on Day 2. Finally, the support vector machine demonstrated that connectivity between the contralateral dorsal prefrontal cortex and the contralateral orbitofrontal cortex were most predictive of early search. **Conclusion:** Together, these results demonstrate that rs-EEG can predict specific motor learning capability in young non-disabled adults.

Disclosures: **A. Hooyman:** None. **J. Kutch:** None. **S. Babikian:** None. **C. Winstein:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 691.21/KK16

Topic: E.04. Voluntary Movements

Support: FWO Belgium

BBSRC UK

Title: A direct effect of perception on action when grasping a cup

Authors: E. ROUNIS[1], V. VAN POLANEN[2], *M. DAVARE[4,3]
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Abstract: Affordances represent features of an object that trigger specific actions. Here we tested whether the presence and orientation of a handle on a cup could bias grasping movements towards it in conditions where subjects were explicitly told to ignore the handle. We quantified the grip aperture profile of twelve healthy participants instructed to grasp a cup from its body while it either had no handle, a handle pointing towards, or away from the grasping hand (3 'move' conditions, with large grip aperture). To ensure the smaller grip aperture afforded by the handle was implicitly processed, we also interspersed trials in which participants had to grasp the cup from its handle or a handle not attached to a cup with a pinch grip. We found that grip aperture was modulated based on both the presence and orientation of the handle in the 'move' conditions. Specifically, grip aperture was smaller when the handle was present, and in particular when it was pointing towards the grasping hand compared to away from it. This suggests that the specific action elicited by an object's attribute can affect movement performance in a sustained manner throughout movement execution.

Disclosures: E. Rounis: None. **V. Van Polanen:** None. **M. Davare:** None.

Poster

691. The Control of Grasp and Grip I

Location: Halls A-C

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Program#/Poster#: 691.22/KK17

Topic: E.04. Voluntary Movements

Title: Prior information triggers differential mirror activity in primary motor cortex of observers even in the absence of kinematic cues

Authors: *A. CRETU, K. RUDDY, M. GERMANN, N. WENDEROTH
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Abstract: Observers are able to infer the action intentions of other people in a seemingly effortless way. Studies using transcranial magnetic stimulation (TMS) demonstrated that the observer's primary motor cortex (M1) becomes facilitated in a muscle-specific manner and that excitability changes are time-locked to the observed kinematics as movements unfold. However, when informative cues are available before an actor initiates the movement, anticipatory motor activity can be decoded from the observer's M1 even before grasping kinematics are visible. Here, we explored whether the muscle-specific modulations occurring in corticospinal activity depend on the type of cue appearing prior to action observation. Furthermore, we were interested in comparing the changes in corticospinal activity elicited when actions are preceded by colored

cues but movement kinematics are not shown at all. To investigate this question, we applied single-pulse TMS to M1 and measured motor-evoked potentials (MEPs) in the index (FDI) and little finger (ADM). Participants observed either whole-hand (WHG) or precision grasping (PG) action videos which were either fully visible or where grasp-specific kinematics were covered. Furthermore, each movement was preceded by an informative cue, which was associated with a certain grasp and which could be used for predicting the upcoming action, or a non-informative cue, which was neutral and could not be associated with any grasp type. To assess the grip-specific modulation present in M1, we compared the change in MEP amplitude across the two muscles, separately for each cue, video type and phase of movement. Our preliminary results show that changes in MEP amplitude are grip-specific when the observed movement kinematics are fully visible confirming previous results. Interestingly, when the grasping kinematics are covered, grip-specific modulation seems to be dependent on the cue type. This suggests that cortico-motor excitability measured in the observer's M1 exhibits grip specific modulation depending on the type of prior information participants receive about the upcoming grip type.

Disclosures: **A. Cretu:** None. **K. Ruddy:** None. **M. Germann:** None. **N. Wenderoth:** None.

Poster

691. The Control of Grasp and Grip I

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Topic: E.04. Voluntary Movements

Support: LSU Biomedical Collaborative Research Program

Title: Changes in brain activation patterns as a result of bilateral transfer of learning of a visuo-motor task

Authors: K. M. KIRBY[1,2], O. T. CARMICHAEL[2], *A. W. VAN GEMMERT[1]
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Abstract: Previous research has shown that training a visuo-motor task with one limb results in performance improvements of the untrained contra-lateral limb (Pan & Van Gemmert, 2013). The performance improvements have been shown to be often asymmetrical, i.e., a greater amount of transfer from one limb to the other limb occurs than vice versa. Although some research has shown some changes in brain activation patterns as result of learning and bilateral transfer of learning, research into brain activation pattern changes as a result of the acquisition of fine motor tasks due to bilateral transfer has been sparse. The current study was designed to add to the limited amount of studies conducted to gain a better understanding of the neural and behavioral correlates of bilateral transfer of learning of a fine motor task. The experiment

required participants to learn a multidirectional point-to-point visually rotated movement task performed with one hand using a joystick. Baseline, acquisition, retention, and transfer tests of the task were all performed in a magnetic resonance imaging (MRI) machine while functional MRI (fMRI) data was acquired. As expected, the behavioral data showed that performance of both the trained and the untrained hand improved over the course of training. Preliminary imaging data showed that brain activation decreased in the frontal lobe over the course of training, while activation increased over the course of training in the occipital lobe. A similar pattern of brain activation changes was found when comparing data from the trained hand before and after training, and when comparing data from the untrained hand before and after training. Although these results are based on a limited amount of individuals and a thus a limited amount of scans, the findings suggest that performance improvements of a visuo-motor task are driven by similar brain activation patterns, no matter whether the improvement is the result of physical practice or not. Future analyses and research will be aimed at determining whether asymmetric transfer of learning performance coincides with asymmetric brain activation patterns.

Disclosures: K.M. Kirby: None. **O.T. Carmichael:** None. **A.W. Van Gemmert:** None.

Poster

691. The Control of Grasp and Grip I

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Program#/Poster#: 691.24/KK19

Topic: E.04. Voluntary Movements

Support: National Science Foundation BCS-1455866

Title: Visuomotor rotation to quantify the impact of vision on grip force control

Authors: *S. TOMA, M. SANTELLO
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Abstract: To prevent object from slipping during object lift, grip force is adjusted in synchrony to the load changes induced by hand motion. Due to unavoidable delays in detecting load force changes by the fingertips, the timing of grip force adjustments need to be planned ahead by the central nervous system with respect to a prediction of when peak load force will occur. This prediction depends on sensorimotor memory built through previously-experienced hand-object interactions. It has been proposed that vision is used before contact to estimate object dynamic, whereas somatosensory signals are used for task-related grip force modulation once the object starts to be manipulated. However, how these modalities might be integrated after contact is not well understood. Here we tested the hypothesis that the contribution of vision for grasp force control can extend beyond contact, and thus influence manipulation performance.
We asked participants to produce ballistic upward (UU) and downward (DD) movements with a

hand-held object while providing a 180°-rotated visual feedback of object motion. This was done to quantify the extent to which grip force would reflect visually- vs. haptically-based predictions of object motion. For the UU condition where the hand moves upward and visual feedback shows downward object motion (UD), we expected peak load force to occur either at the beginning or end of movement based on somatosensory or visual feedback, respectively, and the opposite for DD movements with visual feedback showing an upward object motion (DU). Time to peak grip force during the UD condition occurred later than in UU condition (0.43 ± 0.18 and 0.37 ± 0.12 movement time, respectively; $p < 0.05$) and earlier in DU than DD conditions (0.69 ± 0.13 and 0.76 ± 0.15 movement time, respectively; $p < 0.05$). By removing the effect of rotated feedback on arm kinematics and load force, we found that visual feedback of object motion caused significant changes in peak grip force timing (15% and 10% for UD and DU, respectively). We then quantified the relative weighting of visual and haptic feedback contributions by hypothesizing that changes in peak grip force timing result from a weighted linear combination of the time to peak load force inferred by visual and somatosensory feedback. Surprisingly, we found that the relative weight of vision was sensitive to the direction of visual feedback (0.20 and 0.15 for UD and DU, respectively). Taken together, our findings suggest that the role of vision for grip force control is not limited to the early stages of grasping. Moreover, the observed asymmetry in the influence of vision on grip force control suggests sensitivity to the task context.

Disclosures: S. Toma: None. **M. Santello:** None.

Poster

692. The Control of Grasp and Grip II

Location: Halls A-C

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Program#/Poster#: 692.01/KK20

Topic: E.04. Voluntary Movements

Title: Transcutaneous multi-electrode array nerve stimulation for delayed hand fatigue

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Abstract: Loss of strength and control in the peripheral limbs is a common result of a neurological incident such as a stroke or spinal cord injury. Hand function is especially important for activities of daily living, and restoring hand function is an important focus in rehabilitation engineering. Functional electrical stimulation (FES) is a common technique used to restore the loss of function in paralyzed muscles, but it often leads to quick fatigue of the stimulated muscles. In this study, we examined the force sustainability of a transcutaneous multi-electrode nerve stimulation technique compared to that of a traditional FES technique. Individual load-

cells were attached to the four fingers to record the flexion force of each individual digit. An electrode array was applied on the skin over the ulnar and median nerves underneath the short head of the biceps brachii. Pairs of electrodes that resulted in finger motions were stimulated continuously for 10 minutes to record the change in force level over time. Peak finger force levels were matched with stimulation of the motor point directly over the corresponding finger flexor muscle. The force sustainability was calculated as the mean time it took to reduce to 50% of the original peak force level. Our results showed a prolonged delay in the decrease of the flexion force with the proximal nerve stimulation compared to the distal muscle belly stimulation. This technique has the potential for extending the usability of therapeutic and assistive rehabilitation devices, as well as resulting in decreased comfort.

Disclosures: H. Shin: None. **C. Dai:** None. **X. Hu:** None.

Poster

692. The Control of Grasp and Grip II

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Program#/Poster#: 692.02/DP08/KK21 (Dynamic Poster)

Topic: E.04. Voluntary Movements

Support: R01NS079569

Title: Postnatal motor cortex stroke alters development of the rubrospinal system and proprioceptive afferents

Authors: *P. T. WILLIAMS[1], J. R. BRANDENBURG[1], J. H. MARTIN[1,2]
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Abstract: Cerebral palsy (CP) is a common developmental disorder caused by perinatal stroke. In unilateral CP the corticospinal system (CS) from the damaged cortex fails to develop strong contralateral spinal connections, and the CS from the less affected hemisphere develops bilateral spinal connections and leads to motor map impairments, behavioral deficits, and spasticity. The CS and the rubrospinal system (RS) are two key pathways for skilled limb control, and proprioceptive afferents (PA) provide feedback control. It is unknown if CS miswiring after stroke enhances or corrupts development of the RS or PAs. We addressed two questions: (1) Does motor cortex (M1) stroke alter development of the red nucleus (RN) motor map and pattern of rubrospinal tract (RST) terminations in the cervical spinal cord? (2) Does M1 stroke alter rate-dependent depression (RDD) of the H-reflex and cervical PA axon density. We studied these questions in cats, a species for which we have detailed information about the timing of development of the corticospinal tract, RST, and PAs. Our hypothesis is that M1 stroke produces adaptive augmented growth of the RST and expansion of the RN motor map on the ipsilesional side and maladaptive outgrowth of PAs, leading to hyperreflexia. To model CP, a unilateral

photothrombotic stroke (rose Bengal; 15 min 530 nm illumination) was induced in the forelimb region of M1 at postnatal week 5, a key period of CS and RS development in cats. We examined RST terminations in C8-T1 bilaterally. In terminal experiments at weeks 7-8, the RN motor maps on the ipsilesional and contralesional sides were examined and we assessed RDD of the flexor digiti quinti H-reflex. PAs were labeled with CTB, injected into wrist extensor compartments bilaterally. There was low lesion size variability. All animals showed a contralateral forelimb placing impairment, consistent with M1 lesion. The ipsilesional RN map was larger compared to controls. Surprisingly, the contralesional map was abnormally small with elevated thresholds compared with the ipsilesional side. We found dysregulation of the H-reflex on the contralesional side and an associated increase in PA density. These are the first results to show that CS lesion alters development of the RS and PAs and their functions. The diminished contralesional RS suggests the intact CS out competes the RS for access to spinal motor circuits. The outgrowth of PAs on the contralesional side suggest a maladaptive response leading to dysregulation of the H-reflex. The results highlight the challenge in developing therapeutic strategies for CP, that it is necessary to balance axonal outgrowth and strength across multiple motor and sensory systems.

Disclosures: P.T. Williams: None. **J.R. Brandenburg:** None. **J.H. Martin:** None.

Poster

692. The Control of Grasp and Grip II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 692.03/KK22

Topic: E.04. Voluntary Movements

Title: Age-related differences in white matter integrity and its association with measurements of grasping

Authors: *T. R. VANGBERG[1], O. VASYLENKO[2], S. A. CASTRO-CHAVIRA[2], M. M. GORECKA[2], K. WATERLOO[2], C. RODRIGUEZ-ARANDA[2]
[1]Univ. Hosp. of North Norway, Tromsø, Norway; [2]Dept. of Psychology, Univ. of Tromsø, Tromsø, Norway

Abstract: Background: Older subjects have difficulties in fine motor control of hand dexterity. Degeneration in the neuromuscular system combined with cognitive decline cause movements to become less efficient and slower on both hands during aging. Age-related changes in the CNS may be implicated in these declines. The aim of this study was to investigate the association between the microstructure of cerebral white matter and grasping parameters bilaterally in healthy young and older adults.
Materials: Healthy younger subjects (N=25, 14 males, age 23.0 y), and healthy elderly (N=52, 29 males, age 70.9 y) were tested with the Purdue Pegboard test and video recorded using Vicon

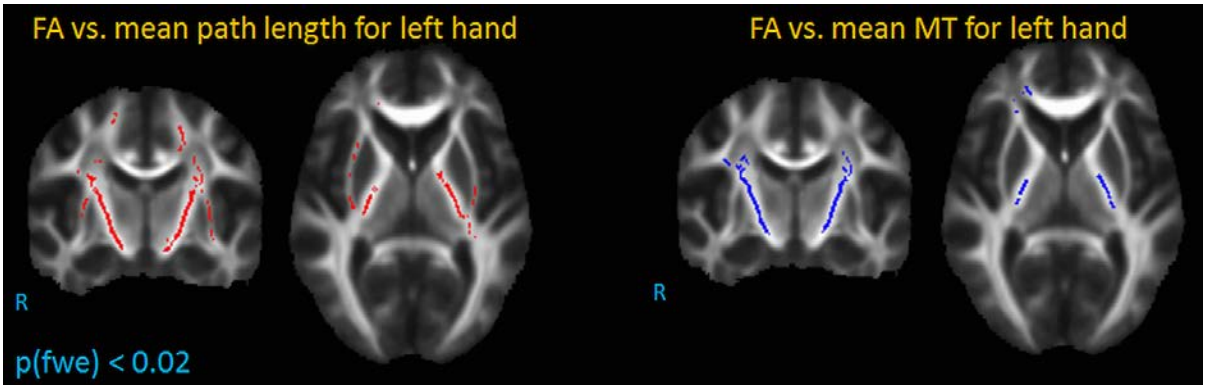
Motus to calculate movement times (MT) and kinematic parameters of grasping. Kinematics included path length, angle and linear and angular velocities. All subjects were right handed. Group differences were found in path length, mean angle and mean MT for grasping. These measurements were selected for each hand (6 in total) and used in the correlation with DTI indices. DTI scans were acquired on a 3T MR scanner. FA and MD maps were processed using tract based spatial statistics. Permutation based statistics were used to assess the association between DTI indices (FA and MD) and each of the kinematic variables, using age and gender as covariates.

Main findings:

• Association between mean path length and mean MT of left hand with FA and MD in left and right corticospinal tract (CST) (Figure).

• Interaction between group and mean time of left hand grasp and FA in the right anterior part of corpus callosum.

Discussion: Only left hand grasp parameters were associated with white matter diffusion indices, which suggests that longer travelled distance and slower movements performed with non-dominant hand are more dependent on age-related changes in the CST than well-learned movements performed with the dominant hand. Data suggest that old subjects primarily influence the association with DTI indices. The significant interaction is found in a region with crossing fibers and may be related to selective degeneration of specific tracts.



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Poster

692. The Control of Grasp and Grip II

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Craig H. Neilsen Foundation Grant 454590

Title: Prolonged time to close the hand during fine grasping after spinal cord injury

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Abstract: Most of our daily tasks involve reach-to-grasp movements with the arms. The extent to which reaching and grasping actions are affected in humans with chronic incomplete cervical spinal cord injury (SCI) remains poorly understood. Using kinematic 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) and movement duration (time between reaction time and grasp) during unilateral self-paced reach-to-grasp movement to a small cylinder in individuals with SCI and age-matched controls. Asymmetries were found in muscle force between the arms of SCI participants, therefore, we refer to the stronger and weaker arm. We found that movement duration of each arm of SCI subjects was prolonged (stronger arm=1.2±1.9 s, weaker arm=1.3±2.6 s) compared with controls (1.0±0.8 s). Although all phases of the reach-to-grasp movement were prolonged in SCI participants compared with controls the increases in movement time were not equally distributed across the arms. Movement time remained similar between arms during arm acceleration (stronger arm=0.4±0.9 s, weaker arm=0.4±0.1 s) and hand opening (stronger arm=0.6±0.1 s, weaker arm=0.6±0.2 s) but it was largely increased during hand closing in the weaker (0.4±0.2 s) compared with the stronger (0.3±0.1 s) arm. Our findings indicate that the ability to grasp a small object is mostly altered at the time to close the hand and contact the object. Hand closing might represent a crucial time for the recovery of grasping following SCI.

Disclosures: **M.A. Perez:** None. **L. Yuming:** None.

Poster

692. The Control of Grasp and Grip II

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Marga and Walter Boll Foundation

UoC EG CONNECT

Title: Neural information processing in motor control during aging

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Abstract: The interest in ageing-related changes of motor performance and the neural basis thereof are governed by the quest for more detailed insights into the possible reorganization of the key phases of an action. For this reason, it is apt and timely to study ageing-dependent effects on the neural organization of motor performance in more detail. The crucial point of such investigations is the study of both, amplitude and phase synchronization, key mechanisms underlying the coordination of distinct neural populations in shaping complex motor tasks.
In earlier EEG-studies on young and older adults, we found that when generating simple finger movements, *local* oscillations in the δ-θ frequencies over the primary motor (M1), the supplementary motor (SMA) and the pre-motor area (PM) exhibited robust phase locking prior to and during the movement. This phase locking represents a trigger of movement preparation and initiation and has no influence on motor performance. We further observed a decrease in post-movement β amplitude synchronization (PMBS) in the medial pre-frontal cortex (mPFC) of older subjects, which may affect the cognitive control of stimulus-induced motor tasks and thereby motor performance.
To further investigate the neural processes underlying age-related dependence of motor performance, we employed *inter-regional* phase-locking analysis by calculating the phase-locking values (PLVs) as well as dynamic causal modeling (DCM) from the EEG records of the two data sets mentioned above. Our analysis revealed significant PLV in both age groups in the δ-θ frequencies around movement onset. Invariant sub-networks were established by strong PLV between brain areas involved in the motor act, which were different in the two groups. Data suggest that older subjects compensate for the diminished contralateral M1 - SMA - ipsilateral PM connectivity during movement preparation and execution by establishing additional intra- and inter-hemispheric connections. The DCM analysis revealed a stronger negative coupling between the β amplitudes of the pre-frontal cortex (PFC) and the mPFC indicating that the strong over-activation of the PFC generally observed in older subjects might be causal for the decreased PMBS in the mPFC.
Based on the above findings, we built a mathematical model consisting of phase oscillators representing main regions of the motor network. This simple model is capable of reproducing the

effects of increased PLI and, independently of this, the effect of increased PLV between both regions.

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Poster

692. The Control of Grasp and Grip II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 692.06/KK25

Topic: E.04. Voluntary Movements

Support: NIGMS-5U54GM104944

Title: The influence of cerebellar transcranial direct stimulation on motor skill acquisition in a complex visuomotor task in parkinson's disease

Authors: *L. LIMA DE ALBUQUERQUE[1], K. M. FISCHER[1], S. JALENE[1], M. R. LANDERS[1], Z. A. RILEY[2], B. POSTON[1]
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Abstract: Cerebellar transcranial direct current stimulation (c-tDCS) is a non-invasive brain stimulation technique that can improve motor performance in hand and arm tasks in young and old adults. However, the ability of c-tDCS to enhance motor performance in Parkinson’s disease (PD) is unknown. Therefore, the purpose was to determine the influence of c-tDCS on motor skill acquisition in a complex visuomotor tracking task in PD. The study was a double-blind, sham-controlled, between-subjects experimental design. Twenty individuals with PD were allocated to either a c-tDCS group or a SHAM stimulation group and each subject completed a single one hour experimental session. Subjects performed a maximal voluntary isometric (MVC) precision grip task and a submaximal visuomotor precision grip task (PGT; practice task) with their most affected hand while on their medications. The PGT involved matching a target sine wave (1 Hz; target force range: 5-35% of MVC) for trials lasting 30 seconds. For the PGT, a baseline block of 5 trials was performed followed by a practice block of 10 trials. The 10 trials were completed over a time course of 25 minutes, which corresponded to the c-tDCS or SHAM stimulation application periods. Anodal c-tDCS or SHAM stimulation was applied over the cerebellum ipsilateral to the primarily affected hand using stimulation parameters that have been proven effective in healthy populations (anode 3 cm to the right of the inion, cathode over the ipsilateral buccinator muscle, 2 mA current strength, 25 minutes stimulation duration) during the PGT practice trials. SHAM stimulation was applied in the same manner according to well-established blinding procedures in which the current was ramped up and down over a 60 second

period. The primary dependent measure of interest was the average force error, which was calculated as the difference in the force produced relative to the target force for each trial and trial block. The force error was similar in the baseline block (P = 0.836) and in the practice block (P = 0.868) for the two groups. The findings indicate that a single application of c-tDCS does not elicit greater improvements in motor skill acquisition compared to practice alone in a complex visuomotor tracking task in PD.

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Poster

692. The Control of Grasp and Grip II

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Topic: E.04. Voluntary Movements

Support: funded by European Commission through MOVE-AGE, an Erasmus Mundus Joint Doctorate Program (2011-2015)

Title: Effects of aging on postural adjustments to visual perturbations during fast pointing

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Abstract: People can quickly adjust their goal-directed hand movement to an unexpected visual perturbation (a target displacement or background motion). An age-related decline in the ability to make the appropriate compensatory postural adjustments might make the manual adjustments of the elderly weaker than those of the young. A decreased resolution of vestibular and proprioceptive information might make their postural adjustments to visual perturbations stronger by making them give more weight to visual information. We therefore examined how aging would affect early manual adjustments and responses of the head and trunk to both types of perturbations, in terms of timing (response latencies) as well as intensity (lateral velocity). Sixteen young (28.3 ± 3.0 yrs) and sixteen elderly (73.9 ± 3.9 yrs) adults participated in our experiment. They were instructed to hit a target as accurately and fast as possible by moving their hand in the sagittal direction on a horizontal screen while standing. In some trials, the target jumped or the background moved in the lateral direction when the hand started to move. We found a similar pattern of manual responses for the young and the elderly, but for the elderly the latencies of the hand were 11 ms longer for both types of visual perturbations. For the elderly, the finger responded 121 ms after the target jump and 133 ms after the onset of background

motion. The response was about 40% smaller than the young for target jumps. The longer latencies for both types of perturbations were also observed for the upper and lower trunk. For the head, we found that neither groups responded to target jumps, but only to background motion. The response magnitude was much larger for the elderly. These results indicate that aging can delay hand responses, and can increase head responses to background motion.

Disclosures: Y. Zhang: None. **E. Brenner:** None. **J. Duysens:** None. **S. Verschueren:** None. **J.B.J. Smeets:** None.

Poster

692. The Control of Grasp and Grip II

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Topic: E.04. Voluntary Movements

Support: Thunder Bay Community Foundation 2015

Thunder Bay Community Foundation 2016

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Title: Changes in muscle activity secondary to a six-week hand training program using a novel concept rehabilitation device

Authors: A. PEPE[1], D. VASILIU[2], B. VOLLEBREGT[3], A. JAIN[4], K. REINIKKA[5], J. LAWRENCE-DEWAR[6], *V. B. JOHNSON[3]
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Abstract: Background & Purpose: Stroke significantly compromises independent finger function. As a result, muscle contraction pattern is altered, with finger and wrist extensor muscle activity inhibited by spasticity, in addition to tightness in the distal flexor muscles. Consequently, ability to perform activities of daily living is compromised. In recent years, the use of robotic devices for hand rehabilitation has garnered interest in the research and clinical community however costs limit their accessibility to patients. This study examined the efficacy of an innovative, low-cost, passive hand rehabilitation device and a custom-structured hand training program designed to improve muscle function in stroke survivors.
Methods: Eight participants (three females) who were at least five months' post-stroke underwent a six-week training program consisting of 18, one-hour classes with a novel hand rehabilitation device. Force, range of motion, speed of contraction and coordination were randomly altered throughout the training process; while visual observation of the on-going task

was prevented to enhance proprioceptive inputs to the cerebellum and cortex. EMG was collected both pre- and post-training from eight muscles, while participants grasped the device to a pre-set resistance, isometrically, for a duration of 30 seconds. The root mean square (RMS) values of the period of muscle contraction were measured. A mixed-groups factorial ANOVA using the LSD procedure (alpha = .05) was used to determine differences between the pre- and post-training program assessments.
Results: A main effect was observed for both muscle ($F_7 = 48.345$, $p < .000$) and time ($F1 = 5.932$, $p = .015$). An interaction effect was observed for the muscle by time factor ($F7 = 2.769$, $p < .008$). This indicated that there was a net decrease in EMG-RMS values over time between pre- and post-training. Pairwise comparisons revealed significant decrease in RMS values for the first dorsal interossei and flexor policis brevis ($p < .05$).
Conclusions: These results suggest that the six-week hand training program resulted in an altered muscle contraction pattern, as observed by a decrease in EMG-RMS values in muscles essential to performing grasp function, accompanied by decreases in proximal muscles that were non-essential to performing grasp function, thereby altering patterns that control hand function. This pilot study provides promising results for the newly designed passive device and the hand function training program. However, results require further testing in a larger population in order to generalize these results.

Disclosures: A. Pepe: None. **D. Vasiliu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); In process to apply for intellectual property protection.. **B. Vollebregt:** None. **A. Jain:** A. Employment/Salary (full or part-time):; SJCG. **K. Reinikka:** A. Employment/Salary (full or part-time):; SJCG & NOSM. **J. Lawrence-Dewar:** A. Employment/Salary (full or part-time):; TBRRI. **V.B. Johnson:** A. Employment/Salary (full or part-time):; Lakehead University. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); 25,000.00 $ CDN from Thunder Bay Community Foundation, 6000.00 $ CDN from Vice-presidents Strategic Fund. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Authors Vineet B K Johnson and Daniel Vasiliu are in the process of applying for intellectual property protection..

Poster

692. The Control of Grasp and Grip II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 692.09/KK28

Topic: E.04. Voluntary Movements

Title: The effects of daily activity on the age-related decline in finger motor function

Authors: *T. AOKI
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Abstract: Purpose: The purpose of the present study was to compare the finger motor function between elderly who were determined to be active for the use of hands in their daily lives (ex. playing musical instruments) (“active elderly subjects”) and who were determined to be inactive in hand use. Methods: Eight active elderly and 9 inactive elderly subjects performed maximum frequency tapping by the index, middle, ring or little finger (single-finger tapping) and with alternate movements of the index-middle, middle-ring or ring-little finger-pair (double-finger tapping). The maximum flexion or extension force by each finger, tactile sensitivity of each fingertip, and time taken to complete a pegboard test were also measured. Results: Compared with the inactive elderly subjects, the active elderly subjects had significantly faster tapping rates in the ring finger in the single-finger tapping and the middle-ring finger-pair in the double-finger tapping. There was no significant group difference in the maximum flexion and extension forces of all fingers, the tactile sensitivities of all fingers and in the pegboard test. Conclusion: Maximum rate of finger tapping was faster in the active elderly subjects compared to the inactive elderly subjects. Thus, the daily activity in elderly adults can be effective in preventing aging in finger motor function evaluated by the tapping test.

Disclosures: T. Aoki: None.

Poster

692. The Control of Grasp and Grip II

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Topic: E.04. Voluntary Movements

Support: T1SK199660

T17K13053

Title: Cortical motor control of reeler mice

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Abstract: The *reeler* homozygous mutants inherently exhibit disorderly positioned corticospinal neurons compared to layered cortical descending projections in a typically developed mouse. The present study investigated the consequence of such a developmentally disrupted cortical lamination on the forelimb motor control in the reeler model, using the neurophysiological, histological and quantitative measures. Using intracortical microstimulation (ICMS), we found evident consequence of the disordered lamina in the mutants, requiring a higher electrical current

to evoke skeletal muscle movements. The current threshold was yielded to be 66.17±8.86μA and 276±73.67μA for the WT and mutants, respectively. No cortical layer-dependency of the threshold alternation may be reported statistically. Upon using different stimulation upper-limits for each group, resulting body representation organization and areal measures were similar. Quantitatively, no significance was detected in the area representing elbow and wrist movements of the reeler (1.37±0.198 mm^2) from that of the WT (1.0±0.09mm^2). Meanwhile no morphological abnormality was observed in the neuromuscular junction (i.e. structure of the acetylcholine receptor) when examined by the immunohistochemistry. Nor the level of choline acetyltransferase was altered when quantified by the western blot. Thus, the functional level of reeler peripheral motor system was comparable to that of the control. Our findings suggest that the mammalian lamina formation represents necessity for proper cortical descending transmission even when the peripheral motor function may be preserved.

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Poster

692. The Control of Grasp and Grip II

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Topic: E.04. Voluntary Movements

Title: A novel method for the prediction of decreased motor performances in the elderly using handwriting characteristics

Authors: *Y. HOSOKAWA[1], K. WATANABE[2], T. WATANABE[2], E. TANAKA[2], T. ANME[2], H. KAWAGUCHI[1]
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Abstract: We aimed to establish a simple quantitative method for the prediction of decreased motor performances in the elderly by analyzing their handwriting characteristics using a digital pen. This device, which digitizes handwriting with resolutions of 0.3 mm and 13 ms, can easily and simultaneously acquire data from many users. Therefore, the digital pen is suitable to screen for the decrease in the motor performances in the elderly.
In total, 138 elderly people (age: 55–92 years; 10 men and 128 women) were recruited for a follow-up cohort study conducted over 4 years (2013, 2014, and 2016) as a part of the Joso project (Elderly People Health Empowerment Project in Joso city, Ibaraki Prefecture, Japan). This project was conducted in cooperation with Joso city, the University of Tsukuba, and Toyo University. The participants were required to complete three questionnaires: lifestyle, basic checklist, and motor fitness scale. These questionnaires included both drawing a figure and the "risk of fall" subscale. The participant's physical and motor functions were also reviewed using parameters such as height, weight, muscle mass, fat mass, blood pressure, abdominal girth, and

grasping power and the one-leg stand test and timed up and go (TUG) test results. Several handwriting characteristics, including writing speed, acceleration of writing speed, stroke range, and writing pressure, were analyzed.
A significant correlation was observed between the acceleration of writing speed and the grip strength in young–old people (age < 74 years, $r = 0.44$, $p < 0.05$). However, a negative correlation was observed between the writing speed and the TUG test result in old–old people (age > 75 years, $r = -0.54$, $p < 0.10$). This implied that people with a higher writing speed exhibited a shorter time in the TUG test result, i.e., they were good at performing complex exercises. Because a significant correlation was observed between the writing speed and the systolic blood pressure in young–old people ($r = 0.35$, $p = 0.10$), we analyzed the systolic blood pressure using binomial logistic analysis. We observed that the writing speed in the first year was significantly associated with the increase in the systolic blood pressure in the fourth year ($p < 0.01$). Some reports have suggested that there is a relationship between an increase in the systolic blood pressure and a decrease in the muscle mass. Therefore, the analysis of writing speed can be useful in the prediction of decreased muscle mass in the elderly. These evaluations might be efficient in maintaining the quality of life in the elderly.
The protocols used in this study were approved by the Ethics Committee of the University of Tsukuba.

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Poster

692. The Control of Grasp and Grip II

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Program#/Poster#: 692.12/KK31

Topic: E.04. Voluntary Movements

Title: Abnormal electroencephalographic oscillations in β and low γ bands in patients with writer's cramp

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Abstract: Writer's cramp is a task-specific focal hand dystonia causing involuntary twitching of muscles preventing patients from writing. Electrophysiological and imaging studies have

identified manifold pathophysiology, including loss of inhibition, exaggerated excitability and deficient sensorimotor integration. As a biomarker of altered sensorimotor processing, abnormal oscillations in electroencephalography (EEG) have been observed during several kinds of tasks. However, recent studies suggested a relevant role of EEG oscillations in other frequency bands, e.g. θ and γ, in the pathophysiology of the disease. The aim of the present study was to explore abnormal EEG oscillations in all frequency bands during the accomplishment of a pen-holding task in writer's cramp. Movement-related EEG (de)synchronization was computed in the 5-45 Hz range in a group of eight patients compared with a group of eight healthy subjects. Between-group comparison of reaction times revealed no significant differences either for movement onset or offset. A robust cluster-based statistical procedure allowed us to identify a few time-frequency bins of EEG oscillations that showed significant between-group differences. First, patients produced smaller and delayed 23-28 Hz desynchronization at the pre-movement period. Second, reduced 13-34 Hz synchronization was seen at the termination of the task in patients. Finally, we for the first time identified 28-45 Hz (low γ band) desynchronization in patients during the execution of movement where healthy subjects showed clear synchronization. As β-band (around 20 Hz) oscillations have been associated with the information flow from the brain to the periphery (i.e. the muscles), impairment at this frequency band has been explained by pathological processes in the cortico-spinal tract, as suggested by previous transcranial magnetic stimulation studies on focal hand dystonia. On the contrary, low γ band has been shown to mainly carry sensory information - locally - within the sensorimotor circuit; consequently, abnormalities of this frequency band can relate to the impaired sensorimotor integration in patients, as previously suggested by means of other electrophysiological techniques. Overall, we provided a revised view about abnormal patterns of EEG oscillations in writer's cramp. Patients with writer's cramp showed abnormal EEG oscillations of both β band (around 20 Hz) and low γ band (30-45 Hz), which appeared at different timings relative to the movement onset and offset. These complex time-frequency EEG abnormal patterns could be further exploited in the future for the design of a new intervention for writer's cramp patients.

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Poster

692. The Control of Grasp and Grip II

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Topic: E.04. Voluntary Movements

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Social Science Research Institute, The Pennsylvania State University

Title: Common neural substrates support visually guided force control and working memory in healthy older adults

Authors: *K. A. NEELY[1], K. A. KURKELA[2], J. T. GOODMAN[2], S. SAMIMY[1], S. L. BLOUCH[1], A. CHENNAVASIN[3], M. T. DIAZ[2], N. A. DENNIS[2]
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Abstract: Advancing age is accompanied by deficits in motor control and cognition that may compromise activities of daily living such as driving, social interaction, and maintaining a daily schedule. Recent work from our group suggests that force control may rely on working memory (Neely et al., 2016, in press). In this study, we sought to determine the overlap in neural activation supporting visually guided force control and working memory in healthy older adults. Further, we aimed to determine whether these tasks elicit similar patterns of increasing neural activity as a function of increasing task demands. To test whether functional activity was domain-specific, a verbal fluency task was included to control for age-related increases in activation associated with task difficulty. Participants (N = 27, ages 60-85) completed three levels of difficulty in each of three tasks (motor, memory, verbal fluency) in one neuroimaging session. In the visually guided force task, difficulty was operationalized by level of target amplitude predictability. In the easy, "static" task, participants produced constant force for 30s to a predictable target. In the medium, "dynamic-same" task, participants produced 2s force pulses separated by 1s of rest to a predictable target. In the difficult, "dynamic-different" task, participants produced 2s force pulses separated by 1s of rest to an unpredictable target. In the working memory task, difficulty was operationalized by a standard n-back task with three conditions: 0-back, 1-back, and 2-back. In the verbal fluency task, difficultly was operationalized by increasing the lexical frequency of the visual stimuli to give rise to three conditions: high, medium, and low lexical frequency. Task difficulty was nested in a blocked-design paradigm consisting of alternating task and rest intervals. A task versus baseline contrast demonstrated that task-relevant brain regions were active during each task. Linear trends related to increasing task difficulty were obtained by modeling each task block using a linear parametric analysis. Subsequently, we employed a conjunction analysis to identify voxels that linearly increased in activity with increasing task difficulty across tasks. The results revealed that no voxels linearly increased as a function of difficulty across all three tasks. However, several areas of overlap were revealed for the motor and memory tasks, including activation in bilateral premotor cortex, right dorsolateral prefrontal cortex, and left supramarginal gyrus. Overlapping activation across the motor and memory tasks supports our hypothesis that both tasks rely on similar neural substrates in healthy older adults.

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Poster

692. The Control of Grasp and Grip II

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Topic: E.04. Voluntary Movements

Title: Grip force control during different manipulative tasks in individuals with diabetic peripheral neuropathy

Authors: *K. C. LIMA[1], G. O. C. SANTOS[3], S. S. V. DONATO[3], P. B. DE FREITAS, JR[2]
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Abstract: The diabetic peripheral neuropathy (DPN) impairs function mainly due to the reduction of sensory input from the feet and especially of the hands. During manipulative tasks, the control system based on somatosensory memory and afferent information from skin receptors (i.e., faster and lower adaptation mechanoreceptors), sets relatively high grip force (GF) than the minimum required to hold the object (safety margin - SM). Recently, our studies showed that DPN reduced the SM compared to healthy individuals during a simple holding task. Whereas we expect the same reduced SM in others more complex tasks (e.g., lifting and oscillation), it is still unknown if other phases that precede or compete with the hold phase the same reduced SM will be seen in DPN individuals. To test this hypothesis, we selected 12 individuals with DPN and compared to 12 healthy individuals (65±1.3 YO) to participate in this study. Firstly, we evaluated cutaneous sensitivity of the five fingers from the dominant hand using the Semmes-Weinstein monofilaments. Next, participants were asked (1) to hold a 6.39 N heavy handle covered with sandpaper (320 grit), using multi-digit grasp, during 10 s and release the handle by slowly opening their digits until slippage; (2) hold and lifting the same object ~5 cm above the table during 22 s; (3) hold and shaking (oscillation task) the same object during 15 s at 1Hz of the frequency. In the first task, the GF mean (GFh) from the holding phase and, the minimum amount of GF needed to hold the object (GFmin) and the relative SM (SMrel) from the slippage phase were calculated [SMrel=100*((GFh-GFmin)/GFmin)]. After, the same equation was used to calculated the SMrel during the lifting and oscillation task. As expected, DPN individuals presented moderate sensory loss in the tip of the digits. Regarding the manipulative tasks, the DPN individuals showed lower SMrel than healthy individuals (91±50% and 181±53% of GFmin, respectively) only during the holding task, showing similar performance in the lifting (224±112% and 287±156%) and oscillation tasks (242±21% and 232±25%), respectively. These results lead us to reject the hypothesis that DPN individuals would set lower SM than controls in more complex manipulative tasks. Apparently, the moderate sensory loss is sufficient to drive the system to an error of GF estimation needed to hold an object, only when the peripheral stimulus is lower and stable (e.g., holding task). When peripheral information is large enough

(i.e., lifting and oscillation tasks), the control system is able to obtain the information and adopt similar strategies of the GF control, maintaining a stable and similar SMrel between DPN and healthy individuals.

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Poster

692. The Control of Grasp and Grip II

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Topic: E.04. Voluntary Movements

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Title: Carpal Tunnel Syndrome intervened with the sensorimotor learning process in unconstrained grip tasks

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Abstract: Carpal tunnel syndrome (CTS) is a compression neuropathy of the median nerve leading to sensory deficits in the affected digits (thumb, index, middle, and the radial half of the ring finger). Our previous work has also revealed motor deficits during manual tasks in CTS patients including excessive large grip force production in whole-hand grasping (Zhang et. al., 2011), reduced ability to modulate digit forces to object mass and mass distribution (Zhang et. al., 2012), and deficits in coordination of CTS-affected and nonaffected digits when engaged in different grip types (Zhang et. al., 2013). The present study was designed to investigate the effect of CTS on anticipatory force control by using a grip device that does not constrain digit position on the object. Ten CTS patients and ten age and gendermatched healthy controls were instructed to grasp, lift, hold and replace a grip device as straight as possible by using either thumb and index finger (2D grip) or all digits (2D and 5D grip, respectively). A hidden weight (200 g) inserted underneath the grip device was used to shift the object center of mass (CM) towards the thumb or finger side (TCM and FCM), respectively. Subjects performed 10 consecutive lifts in each CM condition per grip type (40 trials total). We measured digit forces exerted by the thumb and fingers, as well as object kinematics. Experimental variables were extracted at the time of object lift onset to quantify trial-to-trial learning of anticipatory multi-digit force control. We

found that CTS patients exhibited deficits in multidigit modulation compared with healthy controls, but only early in the early learning stage (trials 23). Moreover, these deficits were found only for grip types that combined CTS-affected and non-affected digits. Specifically, CTS patients exhibited similar grip force to controls, but smaller compensatory moments in 5D at Trial 3 ($P<0.01$) and larger antagonist moment in 5D at Trial 23 ($P<0.05$). These findings suggest that (a) somatosensory deficits induced by CTS may delay sensorimotor learning of hand-object interactions; (b) multi-digit grasping at unconstrained contacts may allow CTS patients to reduce excessive grip force production during manipulations in activities of daily living; and (c) previously reported deficits using CTS-affected and non-affected digits may be due to the greater muscle co contraction than grips using CTS-affected digits only, two or three-digit grips.

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Poster

692. The Control of Grasp and Grip II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Title: Recovered hand function in chronic stroke is related to task based contralesional M1 activity independent of the integrity of lesioned M1 and CST

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Abstract: Stroke often impacts the integrity of primary motor cortex (M1) and its corticospinal projections, resulting in incomplete recovery of hand function. The neuronal substrate supporting hand function in the chronic phase of stroke is not well understood. Abnormally increased activity of contralesional M1 (cM1) is consistently reported in task based fMRI studies of stroke patients moving their affected hand, but its relationship to recovered hand function is still unclear. Here we test the hypothesis that recovered hand function is related to cM1 activity depending on the integrity of ipsilesional M1 (iM1) and CST. Twenty patients (9M, age = 61.7 ± 11.4 years, months since stroke = 31.7 ± 33.0) with partially recovered hand function following stroke involving either M1 or its corticospinal projections completed two runs of cued wrist

extension movements with the affected hand during functional scanning. A single run of eyes-open resting state data was also collected from 19 of the patients. Recovered hand function was assessed with the Jebsen Taylor Test (JTT) and by measuring the peak acceleration of wrist extension movements. Ipsilesional M1 thickness and corticospinal tract (CST) fractional anisotropy (FA) were measured to assess their structural integrity. ROIs were created using the Juelich atlas of motor areas, intersected with the subject's lesion mask where appropriate. Percent signal change (PSC) in the wrist extension task relative to rest was extracted for each ROI. Both measures of hand function (JTT, peak acceleration) were significantly correlated with task activation in cM1. Higher PSC in cM1 was associated with slower peak wrist acceleration and poorer performance on the JTT, even when age was included as a covariate, but iM1 thickness and CST FA did not contribute significantly when included as regressors. We also explored whether task based cM1 activity was related to resting state connectivity between iM1 and cM1. The iM1 seed was created by intersecting the atlas-based iM1 mask with the task based functional activation mask. The amount of correlation between iM1 and cM1 was marginally related to cM1 activity, where patients with a higher iM1-cM1 correlation at rest had more cM1 activity (higher PSC) during the wrist extension task. Our results indicate that in the chronic phase of stroke with injury to M1 or its corticospinal projections, the extent of cM1 activity correlates inversely with recovered hand function independently of the structural integrity of M1 or CST as measured by MRI of the lesioned hemisphere.

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Poster

692. The Control of Grasp and Grip II

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Topic: E.04. Voluntary Movements

Title: Relationship between the performance in the Archimedes spiral drawing and Jebsen and Taylor hand function test in individuals with Parkinson Disease

Authors: *C. C. ALONSO[1], P. B. FREITAS, Jr[3], R. S. PIRES[2], R. B. D. C. GARBUS[4], D. LUSTOSA[4], R. CARNEIRO[5], S. M. FREITAS[6]
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Abstract: Individuals with Parkinson's disease (PD) present several motor impairments that can negatively affect the performance of hand function during daily tasks. The Jebsen and Taylor

hand function test (JTHFT), a clinical test used to characterize the global hand function. Archimedes spiral drawing (ASD) task is generally used to assess the tremor of PD individuals, but if this task could also be used to examine other characteristics of the hand function is still unknown. Therefore, the aim of the present study was to examine the relationship between the performances in the ASD task and the JTHFT of individuals with PD. Twenty-eight subjects, 14 with PD and 14 healthy individuals, right-handed individuals were evaluated. The subjects with PD performed the evaluation under the 'ON' medication and were Hoehn and Yahr stage I and III. Participants performed three trials of ASD task over a digitalizing tablet and one trial of each task of the JTHFT. The order of applied tests was randomized and half of the participants started the tasks with the right hand (dominant) and the other with the left hand. The times to complete the JTHFT tasks and the ASD were recorded. For ASD analysis were also assessed the total displacement (TD) and the displacement and velocity for the anterior-posterior (respectively, Dap and Vap) and medial lateral (respectively, Dml and Vml) directions. Analyzes of variance (ANOVA) were carried for comparison between groups and hands. Pearson's correlations were also carried. The significance value was maintained at 0.05. The time to perform the JTHFT differed between hands and groups and the ASD differed between groups. Interaction was also observed for the variable speed in the ASD. Relation between the JTHFT and ASD was not observed. These findings suggested that although there is no relationship between JTHFT and ASD, both tests are useful for assessing and describing the impairment of the hand function of PD individuals. However, the JTHFT could be a better option as it is more practical for clinical.

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Poster

693. Human Motor Learning: Neural and Clinical

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Program#/Poster#: 693.01/LL1

Topic: E.04. Voluntary Movements

Support: NIH Grant 4R01HD073147-05

Title: Dynamic neural oscillations in the primary motor cortex during retention of motor adaptation

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Abstract: Long-term retention is one of the critical processes of motor learning. Indeed, retention plays an important role in preserving the practiced skill. Neurophysiological and brain imaging evidence suggests that the primary motor cortex (M1) is involved in the formation and

retention of motor memories. We, however, know little about the neural oscillatory and the temporal neural dynamics associated with long-term motor retention. Here, we utilized the high temporal resolution of human electroencephalography (EEG) to investigate the oscillatory dynamics in M1 during retention of recently learned adaptation task. We recorded EEG from M1 in 19 healthy human participants during different learning phases of a visuomotor adaptation task, over two consecutive days. On the first day, participants performed three blocks. In the first block (Rest 1), we recorded brain activity while participants rested for 1 minute. In the second block (Baseline), participants performed rapid reaching movements toward visual targets with full feedback of the cursor. In the third block (Adaptation), participants adapted to a visuomotor perturbation in which the visual curser was shifted 30° relative to their hand. On the second day, which took place 24 hours later, participants performed four additional blocks. In the first block (Rest 2), we recorded brain activity during a minute of rest. In the second block (Retention), participants performed reaching movement with no curser feedback. The absence of feedback allowed us to probe the magnitude of retention per se. In the third block (Washout), participants performed reaching movement with full feedback of the unperturbed cursor. In the last block (Re-adaptation), participants re-adapted to the same visuomotor perturbation as in the first day. For analysis, movements were divided into pre-movement (a time window of 250 ms before movement onset to movement onset) and execution phases (a time window of 250 ms after movement onset). In the temporal domain, we measured event-related potentiation (ERP) locked to movement onset. In the frequency domain, we focused on the power of β [12-30 Hz] and γ [31-85 Hz] oscillations as they have been shown to correlate with voluntary movements and learning processes.We observed increased pre-movement β and γ power during the Retention block compared to Baseline. During movement execution, we observed reduced β activity. We also observed increase in motor event-related responses associated with pre-movement. These data suggest that change in M1 beta and gamma oscillations during retention might be related to retrieval or recall of recently acquired motor memory.

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Poster

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Program#/Poster#: 693.02/LL2

Topic: E.04. Voluntary Movements

Title: Individual differences in adaptation learning are linked to dynamic changes in functional brain states

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Abstract: Learning a new motor skill frequently involves a progression from an initial adaptation stage, which is often error-riddled and highly cognitively demanding, to a less effortful stage marked by an increase in task success. These changes in motor performance are presumed to be mediated by complex interactions between various brain regions and circuits that are continuously changing over multiple time scales. However, our current understanding of the temporal evolution of brain networks over the course of learning and how these relate to behavioural performance remains sparse. Here, using functional MRI (fMRI), we investigated dynamic changes in coupling strength between brain areas and the expression of discrete brain configurations while subjects learned a visuomotor task, from its initial adaptation stages through to plateaus in performance. In accordance with prior work on sequence-based learning (Bassett et al., 2014), we predicted that the recruitment and organization of functional brain networks will change during task performance and that particular features of these dynamics will be correlated to subjects' learning parameters. Twenty-seven subjects, during one continuous fMRI acquisition, performed a visuomotor task that required movement of a cursor from a center target to one of eight possible peripheral targets using a small joystick. After 120 trials, a 45 degree visuomotor rotation--where feedback of the hand cursor was rotated with respect to the hand--was introduced and maintained for another 320 trials. Learning rates for each subject were determined by fitting their movement errors over time with an exponential function. Our analysis of the corresponding fMRI data revealed that although the repertoire of functional brain states was largely preserved across subjects, state-specific temporal features, such as the frequency of expression and number of transitions into particular states, were strongly correlated with task performance. In particular, we found that faster learning rates during initial exposure to the visuomotor rotation were associated with greater connection strengths between visual and sensorimotor areas. Similarly, the frequency of other functional network configurations were also found to be correlated with better initial learning in participants. Together, these results show that individual differences in motor learning is related to dynamic changes in brain network organization and suggest that visuomotor adaptation involves modification of functional coupling strengths between widely distributed brain regions.

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Poster

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Program#/Poster#: 693.03/LL3

Topic: E.04. Voluntary Movements

Support: NICHD R01 HD075740

FRQNT

Title: Reduction in motor evoked potentials following somatosensory perceptual training

Authors: *M. DARAINY, T. F. MANNING, D. J. OSTRY
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Abstract: It has been recently shown that perceptual training—passive arm movement in conjunction with a perceptual discrimination task with feedback, results in an improvement in both the rate and extent of a subsequent sensorimotor adaptation task (Darainy et al. 2013). In a related experiment, a resting state brain connectivity analysis identified functional changes to both sensory and motor area of brain that were associated with perceptual training (Vahdat et al. 2014). We have seen that perceptual training results in changes to motor area of the brain and these changes in motor areas cannot be accounted for by changes, which occur in somatosensory areas. Here we have further investigated the effect of perceptual training on motor function. We used transracial magnetic stimulation (TMS) of brain to measure motor evoked potentials (MEP), a measure of brain motor area excitability. Twenty subjects participated in the experiment and biceps and triceps MEPs were recorded before and after perceptual training. In each case we recorded a block of 30 MEPs using a stimulation magnitude in the middle of each participant's baseline input output curve. Each participant underwent two perceptual training procedures. In the first, the participant's arm was moved passively by a robotic arm to the right or left of the body midline. No response or judgment was required. This was followed by a block of 30 MEPs and then a second perceptual training task. In the second task, the robot again moved subjects' arm passively to one of 10 randomly selected targets that were distributed evenly to the right and left of body midline. In these blocks subjects need to make a judgment as to whether robot moved their arm to the right or left and verbal feedback indicating the accuracy was provided. This second perceptual training task was followed by recording of 30 additional MEPs. As we expected we found no changes to MEP amplitudes following passive movements. In contrast, we found a reduction in biceps MEP following the perceptual training block in which subjects made judgments and were provided feedback. Changes to triceps MEP magnitude did not reach significance but had a negative trend like biceps. A separate group of control subjects did no experimental perceptual manipulation whatsoever. For these subjects we recorded the three blocks of 30 MEPs each. Between blocks subject rested for the duration that experimental group used to do the task. No changes in MEP were found between these three blocks. Our results indicate that passive perceptual training may result in decreases in motor cortical excitability.

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Poster

693. Human Motor Learning: Neural and Clinical

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Topic: E.04. Voluntary Movements

Support: QBIN grant

Title: An acute bout of exercise performed immediately after motor learning alters Beta-band oscillations in the motor cortex

Authors: F. DAL MASO, B. DESORMEAU, A. GHOSH, M. ROIG, *M.-H. BOUDRIAS
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Abstract: Introduction: Performed immediately after motor skill practice, an acute bout of cardiovascular exercise is thought to maximize memory consolidation. This type of exercise has been shown to increase corticospinal excitability, which is associated with motor improvements. Our objective was to use electroencephalography (EEG) to assess how a single bout of exercise modulates corticomotor network neuroplasticity during the initial stages of motor memory consolidation. We hypothesized that a bout of exercise would alter power spectrum of motor cortex (M1) oscillations. Methods: Twenty-six participants were fitted with an EEG cap (BrainVision, 64 electrodes). Data were collected at rest, during the hand-grips as well as during a visuomotor accuracy-tracking learning (AT) task. Then, subjects were taken to the cycle ergometer. The EXE group (n=13) performed a 3*3 min blocks of exercise at 90% of their maximum aerobic power. The CON group (n=13) rested on the bike. Then, resting-state and hand-grip task were repeated at +30 min, +60 min, and +90 min post exercise. The AT task was repeated at +8h and +24h post exercise. Analysis: In this study, we were interested in assessing the effect of group on motor performance gains and the cortical oscillations power spectrum associated with it. Results: All participants improved their motor scores during the practice of the AT task. The EXE participants had greater retention scores at +24h (P=0.021). During the resting-state, beta-band power spectrum density increased in both groups over all scalp areas. This increase was significantly greater in the right M1 for the EXE group (P values ranged between 0.002 and 0.040). During the hand-grip task, Beta-band event-related desynchronization significantly decreased in the left M1 for the EXE group (P values ranged between 0.011 and 0.034). Conclusion: Modulations of M1 beta-band power spectrum suggest that exercise may have altered the level of GABAergic inhibition within both M1. These results suggest that a single bout of intense cardiovascular exercise performed immediately after motor learning triggers neuroplasticity in corticomotor networks of both hemispheres. This observed neuroplasticity may make part of the mechanisms underlying enhancement of motor memory consolidation.

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Poster

693. Human Motor Learning: Neural and Clinical

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Topic: E.04. Voluntary Movements

Support: NIH P01 NS083514-03

Title: Aging does not affect practice-induced increases in beta modulation during a motor task

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Abstract: Movement planning and execution are accompanied by EEG power modulation in the beta range (15-30 Hz) over the sensorimotor area contralaterally to the moving limb: beta power decreases during planning, reaches a minimum during the movement itself and rebounds with a maximum at the movement end. We have shown that in elderly subjects such movement-related modulation increases during one-hour practice block and returns to baseline values when tested 24 hours later (Moisello et al, 2015; Nelson et al, 2017). These practice-dependent increases might represent excitability and plasticity changes of the sensorimotor cortex, which might change with aging.
Here we determine whether: such practice-dependent increases similarly occur in young subjects; beta modulation further increases during several practice blocks; periods of quiet rest re-establish beta modulation to the baseline values; EEG rest activity recorded with eyes opened after each block shows increases in low frequency range.
Therefore, we recorded EEG signal (EGI, 256 electrodes) during one-hour blocks of choice reaction task with reaching movements of the right arm on a digitizing tablet and after each block (2-min eyes-opened resting state) in 26 normal subjects. For each movement, we computed several parameters and movement-related beta modulation over the left sensorimotor area. In a first experiment, young (13, age 22±2.8 yrs) and elderly (13, age 57.5±8.2 yrs) subjects performed the task for one block. While young subjects had a better motor performance ($p<0.01$), both groups showed practice-related increase of movement-related beta modulation ($p<0.001$) without group differences ($p>0.9$). In a successive experiment in 13 young subjects, we found that movement-related beta modulation increased within and across blocks, reaching a plateau by the third block. There were not significant performance changes across blocks. Movement-related beta modulation returned to baseline values after 90 minutes of quiet rest

when tested in a fourth block. Spontaneous EEG recorded with eyes opened after each block showed a progressive specific increase in the low frequency range (<8 Hz) over the left sensorimotor area where movement-related beta modulation was maximal.
We conclude that beta modulation may reflect saturation of cortical excitability and plasticity-related phenomena, as it reached a plateau after 2-hour practice, is not linked to on-line behavioral improvement, left a trace in the spontaneous EEG and re-set after prolonged rest. Also, as beta modulation increases did not depend on age, it is likely that excitability of sensorimotor cortex might not change in the age range we tested.

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Poster

693. Human Motor Learning: Neural and Clinical

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Title: EEG Beta-band modulations in implicit and explicit motor adaption processes

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Abstract: Modulation of human EEG β-band (15-30Hz) oscillations has been originally described in relation to voluntary movement, but since then it has also been extensively described in cognitive tasks requiring sensorimotor interaction, and has received increasing interest in different domains like perception, attention and memory. However, surprisingly β-band activity has been only recently investigated in relation to movement-error processing and motor learning. Tan et al. (2014) demonstrated for the first time that the β-rebound, an increase in β-power at the end of movement, is modulated by kinematic errors. In a previous study (Torrecillos et al. 2015) we found that pre- and post-movement β-activities both are sensitive to kinematic errors, but exhibit different patterns of modulation revealing functional differences. In the present study, our aim is to tease apart the β-band modulations related to implicit adaptation processes from those reflecting the processing of explicit mismatch/surprise, performance feedback and/or reward. We recorded EEG while participants performed a ballistic reaching task in which a visual rotation was unexpectedly introduced in some trials. Participants were

previously trained to use a strategy to compensate for the visual rotation. An explicit reward was provided when the target was hit. First, focusing on the error-related oscillatory responses observed during the foreperiod phase, we contrast two types of trials. On one side, 'after-effect' reaches following directly movements executed under visual rotation, in which the motor command update is automatically triggered. On the other side, trials in which the motor-command update is guided by an explicit instruction, a performance feedback or a reward. Second, focusing on the post-movement period, we compare error-related β-power modulation for reaches in which movement-execution error is induced by an unexpected visual perturbation with trials in which the sensory-prediction error is expected and dissociated for the goal achievement. Third, in the light of previous studies examining β-oscillatory correlates of feedback processing in the context of reward-learning tasks, we examine β-band response to positive reinforcement.

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Poster

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Fonds de recherche du Québec - Nature et technologies (FRQNT)

Banting Fellowship BPF-NSERC-01098

Title: Neurochemical basis for learning novel sensorimotor maps

Authors: ***F. T. VAN VUGT**[1], T. HENNESSY[2,3], J. NEAR[3,2], J. DOYON[4,5,6], D. J. OSTRY[1,7]
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Abstract: One of the puzzles of learning to talk or play a musical instrument is how we learn which movement produces a particular sound: an audiomotor map. Existing research typically uses mappings that are well-learned at the outset such as using a computer mouse to control the movement of a cursor on a screen. Here, we study acquisition of novel sensorimotor maps by having participants learn center-out arm movements to auditory targets. The sounds were not physically localised in space but consisted of oscillators whose frequencies depended in a non-

trivial fashion on the end position of the movement. We previously showed that this mapping can be learned, but the neurochemical bases of this learning are unclear. Here, we acquired functional magnetic spectroscopy (fMRS) over the primary motor cortex hand area while human subjects learned a sensorimotor map. LCModel analysis of MRS data was performed to obtain time resolved measures of various metabolites during sensorimotor learning, including glutamate, glutamine, lactate, N-acetylaspartate (NAA), creatine, choline, myo-inositol, aspartate, and glutathione. Before and after learning, we also obtained resting state functional magnetic resonance imaging (fMRI) scans. In order to assess learning performance, testing blocks were administered before and after learning where participants made reaching movements without receiving auditory feedback to a fixed set of targets, each of which repeated two times in random order. Behaviourally, prior to learning, we found that pairs of participants' movements to the same targets were equally different as pairs of movements to different targets, indicating that they came to this task without prior knowledge. They then showed a marked reduction in reaching error over the course of training indicating that they learned the novel sensorimotor mapping. FMRS revealed increases in lactate and decreases in aspartate concentration during learning, while glutamate showed no significant change. Interestingly, the change in aspartate concentration was significantly correlated with the amount of learning on a subject-level basis, suggesting a possible role of aspartate metabolism in sensorimotor learning. We also assessed changes in functional connectivity at rest between primary motor cortex and other motor and sensory structures that are correlated with the amount of learning. We relate these changes in functional connectivity with metabolic changes obtained using spectroscopy. The present works is a first step towards uncovering the neurochemical basis of changes in brain connectivity in the context of learning novel sensorimotor maps.

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Poster

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Fonds de recherche du Québec - Nature et technologies (FRQNT)

Title: Cerebellum drives motor skill acquisition through online learning and early consolidation

Authors: *N. F. BERNARDI[1], F. T. VAN VUGT[1], R. VALLE-MENA[2], S. VAHDAT[3], D. J. OSTRY[1,2]

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Abstract: The acquisition of skills such as painting or handwriting requires fine control of movement trajectory. However, the neural bases that allow us to learn these skills have been little investigated. Furthermore, studies on the neural basis of motor learning typically focus on either online task performance or on the changes in brain function observable at rest, once learning is complete, but it remains unclear how these two facets of brain plasticity relate to each other. Here we used fMRI to characterize the changes in brain networks that occur as human participants learn to use wrist and finger movements to trace a narrow semicircular path at a prescribed speed. Functional scans were collected during motor learning as well as at rest, immediately before and after learning. We show that in the active phase of learning, motor skill acquisition is accompanied by cerebellar, primary motor as well as prefrontal brain activity and connectivity. Immediately following the task we observed learning-related changes in the spontaneous activity of the brain, involving the connections between the cerebellum, premotor areas and sensory areas, both visual and somatosensory. Our findings provide an account of the changes in brain function throughout the early stages of acquiring a motor skill, suggesting that the cerebellum functions as a hub tying together motor performance, motor learning and early consolidation.

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Title: Individual differences in cortical beta oscillations associated with motor learning

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Abstract: People vary in their capacity to learn and retain new motor skills. Although the relationship between neuronal oscillations in the beta frequency range (15-30 Hz) and motor behaviour is well established, the functional relevance of resting and movement-related beta-band activity for motor learning and retention in humans is incompletely understood.
Here, we investigated the neurophysiological mechanisms underlying inter-individual variability in short-term motor learning behaviour. Since alterations in beta oscillations have been seen with ageing (Rossiter et al. 2014; Heinrichs-Graham & Wilson 2016; Gaetz et al. 2010), and previous studies have suggested an age-related reduction in the potential for plasticity (Tecchio et al. 2008; Fathi et al. 2010; Todd et al. 2010; Chollet 2013), we used the ageing motor system as a model for variations in the balance between inhibition and excitation to examine its behavioural relevance.
Twenty young (18-30 years) and twenty elderly (62-77 years) healthy adults were trained on a motor sequence tracking task and subsequently tested for early (45-60 min) and late (24 hours) retention. Scalp electroencephalography (EEG) during a separate simple motor task was recorded before each training and retention session.
Crucially, we found that pre-training levels of resting beta power from contralateral sensorimotor cortex were correlated with early motor sequence retention ($r = -0.35$, $p = 0.031$), such that subjects with less beta activity prior to training retained more sequence-specific motor skill. Additionally, post-training movement-related beta power from contralateral sensorimotor cortex was associated with early retention of general motor skills, such that subjects with smaller MRBD ($r = 0.29$, $p = 0.073$) and greater PMBR ($r = 0.34$, $p = 0.038$) immediately after training exhibited greater retention. These findings contribute to our understanding of the neurophysiological mechanisms underlying motor learning, and suggest that beta oscillations as potential markers of the net inhibitory and excitatory mechanisms in human sensorimotor cortex are linked to individual differences in the capacity to retain learned motor skills. In the context of disease, beta oscillations may offer novel targets for therapeutic interventions designed to promote rehabilitative outcomes after brain injury.

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Poster

693. Human Motor Learning: Neural and Clinical

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Topic: E.04. Voluntary Movements

Support: CIHR operating grant #125915(LS)

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Title: The effect of concussion on the learning of a novel visuomotor task in elite athletes

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Abstract: Elite athletes are distinct in their ability to learn and perform skilled tasks with greater speed, consistency, and agility relative to non-elite athletes. Previously we have characterized the ways in which elite athletes' learning of a complex eye-hand coordination skill were superior to non-elite athletes (all with no concussion history, CH-), and the sex-related differences in this learning[1] . An issue of increasing concern is the effects of concussion history on skilled performance and motor learning, particularly in asymptomatic young athletes competing at or hoping to compete at elite levels. Recently we have shown that skilled performance can be affected in asymptomatic youth and young adults with a concussion history (CH+) months after deemed recovered by current standards[2-4]. Here we combine and extend these studies by comparing motor learning in an eye-hand coordination task in elite athletes with concussion history (deemed recovered), without concussion history, and CH- non-elite athletes. We characterized the initial and change in kinematics of 69 young athletes (23 CH+ elite, 23 CH- elite, 23 CH- non-elite; 7 females each group; ages 17-28) over multiple trials of learning to navigate a virtual force environment (Phantom™ 3.0 haptic 6D robotic arm) designed as a standard slalom task where the pylons would shift slightly as they were approached[1] . As expected there was a main effect of group on improvement in slalom course movement time ($p<0.05$), mean velocity ($p<0.05$), and mean jerk ($p<0.01$), as well as significantly different variance for these variables between groups. Surprisingly, however, post-hoc analyses revealed no movement time, jerk, or velocity improvement between CH- and control athletes. This was due to an initial worse performance by CH+ athletes. Lastly, mean jerk improvement was lower for CH+ elite athletes. These data show that there are subtle differences in the ability to learn complex skills in young elite athletes with a concussion history, despite being deemed recovered by current standards. 1:McCullough et al.2006, Appl physiol nutr metab,31,S57;2:Hurtubise et al.2016, Concussion1(3) DOI 10.2217/cnc-2016-0006;3:Dalecki et al.2016,Concussion1(3) DOI 10.2217/cnc-2016-0001;4:Brown et al.2015, Oct 19;7:25.

Disclosures: N. Guruparan: None. **J. Hurtubise:** None. **D.J. Gorbet:** None. **L.E. Sergio:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: CIHR MOP 106662

NSERC Grant 2017-04829

Title: Adaptations to novel visuomotor rotations after stroke

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Abstract: Stroke is a leading cause of disability in Canada, where many of the 405,000 adult stroke survivors have long-term disability. Most stroke survivors access neurorehabilitation to improve sensory and motor function. However, little is known about how stroke influences basic mechanisms of sensorimotor learning, and understanding these mechanisms may help improve rehabilitation outcomes. Here we examine motor learning patterns in a task that required stroke survivors and healthy adults to adapt their reaching movements to a novel visuomotor rotation. Experiments were performed with a KINARM exoskeleton robot. Subjects (5 stroke survivors; 21 healthy adults) interacted with a virtual reality system through the movement of their arms. The position of their fingertip was displayed in real time using a white cursor (0.8 cm diameter). We asked subjects to reach back-and-forth between two circular targets (2cm diameter) positioned 10-cm apart. Subjects first completed 25 movements with true feedback of their hand position. We then introduced a 30□counter-clockwise rotation onto the hand feedback cursor to examine how subjects adapted their movements. We unexpectedly removed this rotation after subjects completed 125 movements. Subjects then performed another 25 movements with true hand feedback to examine how they de-adapted their movements. For each trial, we calculated the angular deviation of the hand's path from a straight trajectory between the targets at 150 ms after the onset of movement. Each subject's angular hand path deviations were fit to mathematical models to determine the rate and extent of learning, as well as how this learning was retained from one movement to the next. Group comparisons were conducted using Mann-Whitney U tests. Preliminary analysis revealed marked differences in the learning patterns of stroke subjects and healthy adults. Although the overall extent of learning was similar across groups, stroke subjects required more trials to adapt (>90 trials) their movements to the same visuomotor rotation as healthy adults (<40 trials). Our analysis suggests a reduction in trial-by-trial retention of learning may contribute to the slower learning rates displayed by stroke survivors ($U_{(25)} = 2.35$; $p = 0.0096$). Collectively, our results suggest stroke survivors can indeed adapt their movements to the same overall extent as healthy, age-matched adults. However, this learning is achieved at a slower rate due to a reduction in the amount of learning that is retained from movement to movement. Thus, stroke subjects need to perform many more movement repetitions than healthy adults to adapt to the same visuomotor rotation.

Disclosures: R.T. Moore: None. **S.P. Dukelow:** None. **T. Cluff:** None.

Poster

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The Nakajima foundation

Title: Application of POrtable Motor learning LABoratory (PoMLab): Cross-syndrome comparison of implicit visuomotor adaptation among patients with stroke and Parkinson's disease

Authors: *M. SHINYA[1], K. TAKIYAMA[2], T. SAKURADA[3], S. MURAMATSU[4], H. OGIHARA[5], T. SATO[5], T. KOMATSU[6]
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Abstract: BACKGROUND AND AIM: How to characterize motor dysfunction of patients with neurological disorders is a central question in clinical neuroscience. To measure behavioral data from many patients anytime and everywhere without a huge experimental setup, we have developed a smart device application PoMLab where a cursor on a screen can be controlled by tilting a tablet device (Takiyama and Shinya, PLOS One, 2016). In this study, we compared an implicit adaptation to gradual visuomotor perturbation among patients with stroke and Parkinson's disease (PD). METHODS: Fourteen patients with stroke, 12 patients with PD, 11 elderly control, and 11 healthy young university students are recruited. The patients with PD were in Hoehn and Yahr stages 1 to 4, as evaluated during the on state of their medication cycle. The visuomotor rotation was added by the cursor being rotated with respect to the direction of actual tilt of the device. In our experiment, the visuomotor rotation was gradually increased to 15 degrees, and it gradually decreased to zero so that the participants could not be aware of the perturbation. The adaptation to the perturbation was quantified by calculating a slope of the learning curve. RESULTS: The implicit visuomotor adaptation tested in this experiment was similar among patients with stroke, healthy control elderly participants, and young university students. In contrast, patients with PD showed worse implicit adaptation ability: slower and smaller adaptation comparing with the other groups. CONCLUSIONS: Implicit motor learning mechanisms were intact among young students, elderly control, and patients with stroke. In

contrast, the patients with PD showed worse implicit motor learning than those populations. Although slower adaptation in the patients with PD sounds contradictive to a previous study using an abruptly introduced perturbation (Semrau et al. 2014), our results demonstrate not explicit but implicit components are significantly different in patients with PD. Our results might be consistent with previous findings that patients with PD lack consolidation of the motor memory (Marinelli et al. 2009). These results may be indicative for developing an effective rehabilitation.

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Poster

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Topic: E.04. Voluntary Movements

Support: Donders TopTalent

Title: Fast and slow motor learning processes in Alzheimer's dementia

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Abstract: Motor learning is governed by multiple interactive processes, each with different time constants and sensitivity to errors. Evidence for this is based on a paradigm that evokes spontaneous recovery after learning a visuomotor rotation. The recovery allows inferring a fast process that learns and decays quickly, and a slow process that responds weakly to error but decays slowly. Alzheimer's dementia (AD) is characterized by a decline in declarative memory. While AD patients are still able to learn new motor skills, it is not clear how this learning is achieved. Recently, it has been suggested that the fast motor learning process shares resources with declarative memory processes. Hence, a deficiency in declarative memory should affect the fast, but not the slow process in motor learning. To test this hypothesis, we used a spontaneous recovery paradigm to examine the role of fast and slow learning processes in the acquisition of new motor skills in AD patients (age range 55-80). Participants performed reaching movements to a target while holding the handle of a robotic manipulandum. Visual feedback of hand position (cursor) and target position was provided in the plane of movement. Learning was measured using error clamps and indexed as an adaptation index (AI) representing the fraction of ideal

force compensation. We fitted a two-state adaptation model to capture the time course of the AI. Our first results in healthy age-matched controls are in line with previous observations in the literature, showing evidence for a fast process, which learns and decays quickly, and a slow process, which learns and decays slowly. Experiments and analyses are currently under way to examine how AD patients differ from this behavior.

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Poster

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Topic: E.04. Voluntary Movements

Support: P20GM109098

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T32AG052375

Title: Impaired representation of limb dynamics after stroke

Authors: R. L. HARDESTY, JR[1], V. RAJASEKARAN[2], C. L. ROSEN[2], *V. GRITSENKO[2]
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Abstract: Cerebral infarct, or stroke, is the leading cause of physical disability in the United States. Post-stroke neural damage can result in contralateral paralysis or hemiparesis. While physical and occupational rehabilitation can promote recovery of motor function, long-term residual deficits are common. Even when motion deficits a relatively minor, the muscle activation patterns often differ from age-matched healthy individuals. This may make the impaired movements less efficient and requiring more effort. Therefore, understanding how changes in the neural motor system after stoke alter the muscle activation patterns that lead to movement deficits will help identify interventions that would reduce these deficits. We assessed post-stroke changes in the descending motor pathways using single-pulse transcranial magnetic stimulation of the primary motor cortex (M1). Stroke survivors and age-matched controls reached and pinched visual targets in a virtual reality environment. Targets were located to elicit movements with varying dynamical loads on the limb, i.e. increasing or decreasing gravitational load and assistive or resistive interaction torques between shoulder and elbow. At random times during movement, the M1 was stimulated through a figure-of-eight coil under motion-capture guidance. Motor evoked potentials (MEPs) recorded with electromyography were collected for 15 muscles spanning the shoulder, elbow, wrist, and hand. MEP amplitudes at different times

during movement were used to reconstruct a temporal profile of corticospinal excitability. The temporal modulation of corticospinal excitability was obtained by normalizing MEP amplitudes to the motoneuron recruitment using a linear regression model of static MEPs obtained at different postures. Temporal modulation profiles across muscles were compared using a regression analysis and hierarchical clustering of correlation matrices. Stroke survivors showed decreased temporal modulation of corticospinal excitability compared to age-matched controls, particularly in tasks with resistive interaction torques and increasing gravitational load. These results suggest that altered muscle activation patterns leading to residual motor deficits after stroke may be the result of dysfunctional representation of limb dynamics in the impaired descending motor pathways.

Disclosures: **R.L. Hardesty:** None. **V. Rajasekaran:** None. **C.L. Rosen:** None. **V. Gritsenko:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: NIH (NCMRR) 1R01HD075813-01A1

Title: Use of a EMG-controlled game as a therapeutic tool to retain hand muscle activation patterns following stroke

Authors: M. GHASSEMI[1], A. BARRY[2], K. TRIANDAFILOU[2], M. STOYKOV[2], *D. G. KAMPER[3], E. ROTH[2]
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Abstract: Aberrant muscle activation patterns constitute one of the primary mechanisms of hand impairment following stroke. Individuals with chronic hemiparesis typically exhibit an inability to fully activate a desired muscle, to deactivate the muscle once excitation begins, and to modulate muscle activation patterns with task. The region of the activation workspace which they can voluntarily attain is often quite limited. To encourage exploration and expansion of the activation workspace, we developed a custom computer game that is electromyographically (EMG) controlled. Specifically, principal components (PCs) describing the accessible activation workspace are mapped to the axes of the computer screen, with one PC representing the vertical direction and one PC representing the horizontal direction. The user must create scaled combinations of these patterns to move the cursor in order to reveal pictures, traverse through mazes, or gather coins to play a game based on Asteroids. This system is being used as part of an

ongoing longitudinal intervention study for stroke survivors with severe hand impairment, as rated Stage 2-3 on the Stage of Hand section of the Chedoke-McMaster Stroke Assessment scale. One cohort of the study participants focuses on training activation patterns, by alternating between use of the EMG-controlled game and an EMG-controlled active hand orthosis. So far, 8 individuals from this cohort have completed the treatment, which includes 9 sessions (45 minutes each) with the EMG-driven game over 6 weeks. For each subject, PCs from the unimpaired hand were introduced as the target PCs for the impaired hand over the 9 sessions and difficultly was gradually increased by expanding the required range of the desired PC. Preliminary results showed a 4.8 ± 7.6 min decrease, equal to 25% of the total value across subjects in average time to complete the task from the second day to the ninth day of training. These findings demonstrate that stroke survivors with even chronic, severe impairment can learn to improve control of muscle activation patterns. Assessment of translation to functional hand use is ongoing.

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Poster

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Topic: E.04. Voluntary Movements

Title: Age-Related differences in controlling a robot arm

Authors: *M. R. PADMANABHAN
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Abstract: A fundamental question in motor development examines whether or not children and adults learn motor skills differently, especially when learning a novel motor task. In previous studies, we found age-related differences in movement performance and coordination in a 2-dimensional cursor-control task. In this study, we further investigated the generality of these age-related learning differences by changing the task in two ways (i) controlling a robot arm, instead of a cursor, in 2-dimensions, and (ii) using velocity-control instead of position-control. Participants' shoulder movements were measured using 4 inertial measurement units (IMU) and these movements were mapped to the velocities of a robot end-effector. Participants learned to control the robot arm by reaching to distal targets that were placed equidistant from a center target. Both children and adults practiced for a total of 72 trials reaching toward 4 targets in the cardinal directions. To examine the generalization, we also included three tests (pre, during and post-practice), where participants reached toward 4 additional targets in the diagonal directions. Principal Component Analysis (PCA) was used to perform the dimensionality reduction. Results showed that age-related differences in learning continue to exist in this framework.

While 96% of adults and 67% of 12-year-olds were able to complete the task, only 27% of 9-year olds completed the task. Adults and the 12-year-olds did not have significantly different movement times and path straightness to the targets, which differs from previous results. Additionally, we examined movement exploration by running a PCA of the sensor signal data and comparing the percent variance explained by the first two principal components. The adults showed a decrease in movement exploration throughout the task while the 12-year-olds exhibited similar exploration throughout the duration of the task. These results suggest that there may be age-related differences in the way a novel task is learned. These results have implications for structuring practice schedules in children, especially pediatric rehabilitation.

Disclosures: M.R. Padmanabhan: None.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

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Topic: E.04. Voluntary Movements

Support: R01 AG041878

Title: Understanding the relationship between exploratory variability and learning ability by dissociating the effects of persistence versus task relevance for motor variability

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Abstract: Variability in the motor system has been found to predict motor learning ability across individual subjects and tasks (Wu et. al, Nat. Neurosci. 2014). However, this result is still controversial (He et. al, PLoS Comp Bio 2016) and variability is not monotonic, so that specific components of variability may underlie the relationship between motor variability and motor learning. One way to parse variability is into variability that occurs in task relevant vs task irrelevant (i.e. redundant) dimensions. A second way to parse variability is based on accumulating versus non-accumulating components. Accumulating variability displays persistence and will thus act like a drifting random walk process in that current variability builds upon previous variability, resulting in a strongly positive autocorrelation. In contrast, non-accumulating does not persist and will thus act like a white noise process in that current variability is independent of previous variability, resulting in near-zero autocorrelation. A recent study (Singh et. al, PNAS 2016) suggested that baseline variability only in the task-irrelevant dimension is predictive of the learning rate of the task. However, it is known that task-irrelevant variability displays large positive autocorrelations corresponding to a drifting, random-walk-like behavior, like that observed in cortical areas that control movement. In contrast, task relevant

variability does not display these high autocorrelations, because feedback in task relevant dimensions allows motor adaptation to compensate for these drifts to reduce errors. Thus, task relevant feedback in the baseline period can obscure the ability to measure the random-walk-like accumulating variability that would occur without feedback-driven motor adaptation in task relevant dimensions, and which may correspond to the centrally driven component of task relevant motor variability. We thus devised an experiment to allow us to determine whether motor learning ability is predicted better by sources that drive random-walk-like accumulating variability versus sources that drive variability in task relevant dimensions per se. We thus simultaneously measured, in a baseline period without feedback, both non-accumulating (white noise) and accumulating (random-walk-like) components of motor variability in dimensions that would be irrelevant to subsequent motor learning versus in dimensions that would be task-relevant to motor learning. This enables us to dissect the relationship between motor variability and motor learning ability based on both task-relevant vs irrelevant dimensions and accumulating vs non-accumulating variability sources.

Disclosures: **T. Ranjan:** None. **M.A. Smith:** None.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

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Support: NICHD R01 HD075740

Fonds de recherche du Québec - Nature et technologies (FRQNT)

Title: The relation of proprioceptive working memory to human motor learning

Authors: ***A. SIDARTA**, F. T. VAN VUGT, N. F. BERNARDI, D. J. OSTRY
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Abstract: The capacity to maintain in working memory previously performed movements, and their success or failure, presumably plays a substantial role in motor learning. Indirect evidence to this idea come from a recent study in which we found that motor learning correlates with changes in functional connectivity between second somatosensory cortex (SII) and BA 9/46v (lateral prefrontal cortex), the latter being known to contribute to somatosensory working memory (sWM). In the current study, we directly tested the hypothesis that there would be a correlation between proprioceptive sWM and human motor learning. We designed a behavioral task which is a variant of an N-back procedure to assess such working memory. On each trial a robotic device displaced the participants arm in a number of different directions (memory set),

and was followed by a test displacement that was used assess working memory. On half of the trials, the test direction was one of the items in the memory set, and in the other half it was not. Participants had to indicate whether or not the test movement was from the memory set. We expected that response accuracy would decay for items in the memory set being presented longer ago and that this decay measured sWM capacity. A memory curve was computed as the proportion of Hits minus False Alarms as a function of number of movements separating the test item and to-be-remembered item (lag). On a separate day, the same subjects performed a motor learning task in which they made reaching movements to hidden targets and received positive reinforcement when they were successful. Overall, we found that subjects that had better sWM learned more in the motor learning task ($r = 0.51$, $p < 0.05$), suggesting the involvement of sWM in motor learning. The correlation is the strongest for lag-1 ($r = 0.53$, $p < 0.01$). The findings suggest a contribution of proprioceptive working memory to human motor learning. This knowledge enhances our understanding on the role of somatosensory information in the initial stages of motor learning.

Disclosures: **A. Sidarta:** None. **F.T. Van Vugt:** None. **N.F. Bernardi:** None. **D.J. Ostry:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: NSF Grant 1342962

Title: Proprioceptive changes following complex motor skill learning

Authors: *J. L. MIRDAMADI[1], H. J. BLOCK[1,2]
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Abstract: Motor skill learning entails changes in behavior through practice. It is well established that this process involves plasticity in motor regions, including primary motor cortex and the cerebellum. However, recent literature suggests that multiple types of motor learning influence sensory processing and are associated with plasticity in somatosensory cortex. For example, trial-and-error motor adaptation shifted hand position sense or proprioception (Ostry et al., J. Neurosci., 2010), and center-out reaching practice enhanced proprioceptive acuity (Wong et al., J. Neurophysiol, 2011). Whether such changes occur when learning a novel complex motor skill is unclear. In contrast with motor adaptation, motor skill learning involves acquisition of new movement patterns in the absence of a perturbation and an overall enhancement in movement quality. Here we asked whether proprioception improves in association with motor skill learning

in the upper limb. The motor skill was a track-tracing task that involved navigating a cursor using a robotic manipulandum handle (McGrath & Kantak, Hum Mov Sci, 2016). Subjects were instructed to move the cursor through an irregular-shaped track as accurately as possible within a prescribed movement time range. Total length of the track was 20 cm, and visual feedback was provided to encourage subjects to prioritize movement speed. Participants practiced the motor skill on two consecutive days. Performance was assessed through changes in accuracy (percentage of the subject's movement path that was within the track). On the third day, there was a retention test where learning was assessed through a shift in the speed-accuracy function relative to baseline performance. On each day, we quantified proprioception in the hand relative to a visual reference using an adaptive staircase algorithm. Preliminary data (n = 4) suggest that practice improved motor performance during training and enhanced the speed-accuracy tradeoff function at retention. Furthermore, proprioceptive bias and sensitivity were improved following a single session of training. However, these proprioceptive changes did not persist at retention. These findings have important implications for the role of proprioception in motor control and learning. Specifically, improvements in proprioception may be important for complex motor skill learning.

Disclosures: J.L. Mirdamadi: None. **H.J. Block:** None.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

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Topic: E.04. Voluntary Movements

Title: An experimental investigation of the role of spatial working memory in age-related declines in working memory

Authors: *L. RAJESH KUMAR[1], K. M. TREWARTHA[2]
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Abstract: Motor learning is supported by the combined influence of a fast process that allows for rapid improvements in performance, and a slow process that allows more gradual improvements. Research has shown that age-related declines in working memory are associated with impairments in the fast component of motor learning. However, the precise nature of the working memory mechanisms underlying age-related changes in the fast process for motor learning is unclear. The current project was designed to investigate whether spatial working memory resources in particular, underlie age-related declines in the fast component by manipulating spatial working memory load during a motor learning task. A group of older adults (60 to 85 years old), and a group of younger adults (18 to 30 years old) gradually learned to adapt their arm reaching movements to a clockwise or counterclockwise curl-field applied by a

robotic device (KINARM, BKIN Technologies). Participants from each age group were randomly assigned to a high or low working memory load condition and made center-out reaching movements to four visual targets. In the high load condition the order in which the targets were presented was randomized, whereas in the low load condition the targets appeared in a repeating four-target sequence. Participants also performed a cognitive battery that allowed us to evaluate the correlations between the fast process for motor learning and spatial working memory, associative working memory, and implicit memory resources in younger and older adults. The first aim of this project was to determine whether younger and older adults were differentially affected by the manipulation of spatial working memory load during the motor learning task. We tested the hypothesis that older adults would benefit less from the reduced working memory load condition compared to younger adults. The second aim was to test the hypothesis that the fast process for motor learning is more related to spatial than associative working memory in the older adults. Combined, the current data contribute to our understanding of the memory mechanisms underlying motor learning, and the nature of age-related changes in those memory processes in later adulthood.

Disclosures: L. Rajesh Kumar: None. **K.M. Trewartha:** None.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 694.05/LL21

Topic: E.04. Voluntary Movements

Title: Mental workload and motor performance assessment during practice of reaching movements under various task demands

Authors: *I. SHUGGI[1], H. OH[2], P. A. SHEWOKIS[3], R. J. GENTILI[1]
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Abstract: Numerous studies have focused on assessing mental workload to inform how attentional resources are allocated during task performance, which is critical for understanding the underpinning mechanisms of human cognitive-motor behavior. Although a large body of work has examined mental workload in a context of motor performance, a limited number of studies have investigated mental workload during motor practice/learning. Specifically, no prior work has examined the relationships between mental workload and the rate of motor improvement during practice while also considering individual differences. Therefore, the aim of this study was to assess the concomitant variations in mental workload and motor performance resulting from practicing novel reaching movements by manipulating the level of task difficulty. Through a human-machine interface, individuals had to learn to control a virtual robotic arm to

reach targets that were randomly located in a 2D workspace. Participants were assigned to one of two groups, where they performed the task at either a low or high level of nominal difficulty. Nominal difficulty level was determined by the robotic effector's velocity. Surveys and arm kinematic data were analyzed to assess cognitive workload and motor performance, respectively. Mental workload, motor performance and motor improvement dynamics were analyzed by employing a traditional group-level analysis complemented by a cluster analysis to detect specific individual patterns of cognitive-motor responses. Both group-level and cluster-level analyses revealed that performance improved during practice and that an elevation of mental workload resulted in performance deterioration accompanied by slower motor improvement. Considering the optimal challenge point theory, this work suggests that the functional task difficulty: i) partially depends on the nominal difficulty level as well as on the individual's information processing capabilities, and ii) could be assessed via the level of mental workload, which when excessive can lead to performance degradation as well as a deceleration of motor improvements. Currently this work is being extended through the use of EEG to assess the attentional reserve and cortical effort, which can collectively index the cognitive workload during motor practice and learning. Overall, this work can inform human cognitive-motor processes as well as assist in the design and practice parameters associated with assistive technologies and prostheses.

Disclosures: I. Shuggi: None. **H. Oh:** None. **P.A. Shewokis:** None. **R.J. Gentili:** None.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

Location: Halls A-C

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Program#/Poster#: 694.06/LL22

Topic: E.04. Voluntary Movements

Support: NSERC

DFG HA 6861/2-1

Title: Older adults benefit less from explicit instruction, but show a larger change in perceived but not predicted estimate of hand position following visuomotor training

Authors: *C. M. VACHON[1], S. MODCHALINGAM[2], B. M. T'HART[3], D. Y. HENRIQUES[4]
[1]Psychology, [2]Kinesiology and Hlth. Sci., York Univ., North York, ON, Canada; [3]Psychology, York Univ., Toronto, ON, Canada; [4]Dept Kinesiol & Hlth. Sci., York Univ., North York, ON, Canada

Abstract: Our brains are very successful at adapting our motor movements to a wide array of changes, including bodily changes due to senescence. Such adaptation of skilled movements to

changes is thought to rely on sensory estimates of errors. Despite decreased sensory capacity with aging, some studies have shown intact motor learning in older adults compared to younger adults. It is unclear how older adults maintain task performance on some motor tasks and not others. Two possible explanations are that older adults compensate for sensory decline by relying more on (1) efference based estimates of hand movement, and/or (2) explicit, cognitive strategies. In the current study we compared how older (n=17) and younger (n=43) adults responded to instruction (provided to half of each group) on how to compensate for a 30º visuomotor rotation during training and afterwards when reaching without a cursor. We also compared training-induced changes in proprioceptive and predicted estimates between these two age groups. We did this by having all four groups, both before and after visuomotor adaptation, estimate the location of the unseen hand when the hand was moved out by the robot (passive localization) and when the hand was moved by the participant themselves (active localization). The difference between these two estimates roughly reflects changes in predicted or efferent-based estimates, whereas the passive localization should reflect mostly proprioception. Older adults benefitted less from instructions during initial training with the rotated cursor. Following visuomotor adaptation, older adults showed larger visually-driven changes in their passive or proprioceptive - but not their efference-based or predicted - estimates of hand position. This indicates that older adults appear to visually recalibrate felt hand position more than younger adults. Our preliminary results suggest that rehabilitation for older adults should focus less on explicit instructions, but rather on training that emphasizes visual feedback.

Disclosures: C.M. Vachon: None. **S. Modchalingam:** None. **B.M. t'Hart:** 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.; DFG HA 6861/2-1. **D.Y. Henriques:** 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.; NSERC.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 694.07/LL23

Topic: E.04. Voluntary Movements

Support: NSERC

DFG HA 6861/2-1

Title: Is proprioceptive recalibration explained by a multi-rate model?

Authors: *J. E. RUTTLE, B. ’T HART, D. HENRIQUES
York Univ., North York, ON, Canada

Abstract: A powerful model for motor learning combines a fast and slow learning process (Smith et al., 2006). It can be extended to visuomotor adaptation, with explicit and implicit learning representing the fast and slow process, respectively (McDougle et al., 2015). After adaptation to a visuomotor rotation we also observe a shift in felt hand location; 'proprioceptive recalibration'. Here we investigate if a multi-rate learning model can explain proprioceptive recalibration, specifically, if recalibration maps onto the slow or fast process in reach adaptation. We test this with two visuomotor adaptation paradigms, with the same four phases using varying visual feedback of the hand, modelled after earlier experiments: 1) aligned training, 2) prolonged rotation training, 3) brief opposite rotation training, and 4) error-clamp training. During error-clamp trials the cursor moves straight to the target, regardless of actual reach direction, removing movement error signals. In this phase, reach output should rebound to what the slow process has retained from the prolonged training phase. One of our paradigms includes a localization trial after each reach training trial, to measure proprioceptive recalibration on a trial-by-trial basis. In localization trials, a robot moves the unseen, trained right hand to a location close to the previous training target. Participants then indicate the felt location of their right hand on a touchscreen, using their visible, untrained, left hand. A visual arc demarcates the correct distance from the start position. In the second paradigm, localization is replaced with a pause. A two-rate model predicts reach directions fairly well (RMSE=2.88°, R^2=.837), including the rebound in the error-clamp phase. The trial-by-trial data suggest that proprioception recalibrates extremely fast. AIC analysis shows that this does not follow the time course of either the slow or fast process of the reach model (both $p<.0008$). Modelling localization change as a proportion of the visuomotor rotation from the preceding reach trial gives the best fit, but this is indistinguishable from a single-process ($p=.393$) or two-process ($p=.052$) model of localization. When comparing reaches across paradigms (localization vs. pause) the time course of learning and values for each parameter were similar with localizations only reducing the fast retention rate ($p_{fdr}=0.15$). It remains unclear how to model proprioceptive recalibration and its effects on reach adaptation. It is clear that proprioceptive recalibration does not merely reflect an aspect of motor changes, and should be considered an independent process in motor learning.

Disclosures: J.E. Ruttle: None. **B. ’t Hart:** 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.; DFG HA 6861/2-1. **D. Henriques:** 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.; NSERC.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 694.08/LL24

Topic: E.04. Voluntary Movements

Support: NSERC

DFG HA 6861/2-1

Title: Explicit awareness of a perturbation during training does not affect predicted and perceived sensory consequences of hand motion

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Abstract: Explicit awareness of a task is often evoked during rehabilitation and sports training with the intention of accelerating learning and improving performance. However, the effects of awareness of perturbations on the resulting sensory and motor changes produced during motor learning are not well understood. Here, we use explicit instructions as well as large rotation sizes to generate awareness of the perturbation during a visuomotor rotation task and test the resulting changes in both perceived and predicted sensory consequences as well as implicit motor changes. We split participants into 4 groups which differ in both magnitude of the rotation (either 30° or 60°) during training, and whether they receive a strategy to counter the rotation or not. The effect of explicit instruction seems limited to an initial error-reduction advantage of ~20°, regardless of the size of the perturbationWe show that with instructions, and also with large perturbations, participants are aware of how they counter the rotation. This allows them to apply a strategy at will in open loop reaching tasks following training. However, when asked to exclude the strategy, none of the four groups can entirely exclude learning, implying a base amount of implicit learning (~15°) which is present in all groups, regardless of strategy use or rotation magnitude.Also following visuomotor adaptation, participants estimate the location of the unseen hand when it is moved by the robot (passive localization) and when they generate their own movement (active localization). By comparing the differences between these hand estimates after passive (only proprioception) and active (both proprioception and efferent-based prediction) movements, we are able to tease out a measure of predicted sensory consequences following visuomotor adaptation. These estimates of felt hand position and predicted sensory consequences change to a similar extent independent of whether participants receive instructions or not. Our results indicate that although some aspects of motor learning are affected, not all processes

benefit from an explicit awareness of the task. Particularly, proprioceptive recalibration and the updating of predicted sensory consequences are largely implicit processes.

Disclosures: S. Modchalingam: None. **C.M. Vachon:** None. **B.M. 't Hart:** 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.; DFG HA 6861/2-1. **D.Y. Henriques:** 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.; NSERC.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

Location: Halls A-C

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Program#/Poster#: 694.09/LL25

Topic: E.04. Voluntary Movements

Support: NIH K12HD073945

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Title: Motivational state influences motor adaptation

Authors: *J. GALARO[1], A. DIZENZO[2], D. MCNAMEE[3], V. S. CHIB[1]
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Abstract: We have the remarkable ability to learn a myriad of motor behaviors in a variety of contexts. From skipping down the street to swinging a golf club, we are able to learn to control our movements to perform complex actions - but how does our motivation impact motor learning? Current theories regarding motor learning posit that reduction of motor error drives motor adaptation; recent work has indicated that other variables, such as action-contingent rewards/punishments modulate the learning process. In this study we tested whether a person's internal motivational state influences the manner in which they learn to control their movements by applying a well-established classical conditioning paradigm to a motor control task. More specifically, we examined how motor learning of a novel dynamical environment (a force-field perturbation) is influenced by the concurrent presentation of Pavlovian conditioned stimuli (CS). These stimuli were fractal images that had been previously presented in association with either

high ($30, CS+) or low ($10, CS-) monetary rewards. Participants then performed a force-field learning task during which the conditioned stimuli were presented on screen. The motor learning task involved making center-out movements while grasping the handle of a planar manipulandum rendering a velocity-dependent curl field. Each of the conditioned stimuli (CS+ and CS-) were presented on 50% of the trials, pseudo-randomly interleaved. Critically, rewards were only delivered during the Pavlovian association phase and no rewards were contingent on the action being performed. This allowed us to examine how motivational state, independent of and uncorrupted by the effects of reward, influences motor adaptation. We found that learning was significantly faster in the higher motivational state CS+ condition compared to the CS- condition. This manifested in larger decreases in maximum perpendicular error and increases in mean performance rate. Control conditions in which the Pavlovian rewards were matched in magnitude resulted in no significant differences in motor adaptation. Furthermore, we analyzed our data using a hierarchical mixed effects model in order to observe how prediction error and kinematic update measures interact to result in enhanced learning. Applying a reward prediction error model gated on the motivational state condition showed that participants had an increased update weight for trials performed in the CS+ condition as compared to the CS- condition. Our results indicate that an enhanced motivational state increases the degree to which individuals update their motor plans, and that these invigorated updates amplify motor learning.

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Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: E.04. Voluntary Movements

Support: Ramanujan Fellowship

DST Cognitive Science Initiative

DST Extramural

Wellcome Trust/India Alliance

Title: Selective suppression of adaptation to motor errors irrelevant to task success

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Abstract: Human arm movements appear to be planned as vectors with independent specification of direction and extent. According to this framework, errors in direction and extent must be differentially processed when adapting our movements to varied task conditions. We tested this hypothesis and predicted that if these two errors are processed independently, subjects should selectively suppress adaptation to one of them if it is irrelevant to task success. Seven groups of subjects adapted to three perturbations: rotation alone, gain alone or rotation+gain. The rotation and gain induced direction and extent errors respectively. Error relevance was manipulated by having subjects reach to an arc or a bar; direction errors were irrelevant for the arc but not the bar and vice versa for extent errors. Adaptation was assessed via catch trials requiring reaches to a point target. Rotation and gain adaptation was evident during reaches to the bar and the arc. Thus, error relevance did not matter in the rotation alone or gain alone conditions. Remarkably however, in the rotation+gain condition, we observed a striking double dissociation. Subjects showed no rotation adaptation when reaching to the arc, and no gain adaptation when reaching to the bar. That is, adaptation to a perturbation that was irrelevant to task success was selectively suppressed when it was presented simultaneous with another that was relevant to task success. Control conditions confirmed that the observed suppression was not due to an inability to adapt to two simultaneously imposed perturbations. These results thus strongly support the idea that movement direction and extent are independently processed in the brain.

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Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

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Program#/Poster#: 694.11/LL27

Topic: E.04. Voluntary Movements

Support: JSPS Grant-in-Aid for Young Scientists B (16K16122)

Title: Influence of switching rule on motor learning

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Abstract: Humans can flexibly generate different behaviors for an identical sensory stimulus, e.g., we kick a soccer ball towards a friend who belongs to our team but we kick the soccer ball far away from the friend who belongs to an opposing team. This relation between sensory stimuli and responses is referred to as Stimulus-Response map (S-R map). The abovementioned example indicates our ability to flexibly switch between congruent S-R map (movement direction is towards a visual stimulus (i.e., a friend)) and incongruent S-R map (movement direction is far

away from a visual stimulus). In other words, we can flexibly switch a rule to generate appropriate motor commands.
Conventional motor learning theories depend on goal-directed reaching movements, or the congruent S-R map (Thoroughman & Shadmehr, 2000, Nature, Donchin et al., 2003, JNS). Those theories indicate that planned movement is a principal factor to affect motor learning. Although the same movement can be planned in different rules, e.g., kicking the ball towards rightward direction when a friend in our (opposing) team is in the rightward (leftward) direction, it is unclear whether we can show the same motor learning effect when the planned movements are the same but the rule is switched.
Here, we investigated how switching rule affected motor learning based on pro- and anti-reaching tasks (Riehle et al., 1994, Neuro Rep, Klaes et al., 2011, Neuron). In the pro-reaching task, subjects were instructed to reach towards a visual target. In contrast, subjects were instructed to reach towards opposite direction of a visual target in the anti-reaching task. First, our findings indicated that switching rule affects motor learning even when planned movements are the same; transfer of learning effects from pro- to anti-reaching movements was 75% when the planned movements were the same. Second, we proposed several candidates of computational models to explain this result: 1) a model in which aimed movement directions in anti-reaching show fluctuation in each trial, 2) a model in which neural activities in anti-reaching movements are smaller than those in pro-reaching movements, and 3) a model in which the height of tuning curve is different between pro- and anti-reaching. Third, for dissociating the predictions of those models, we investigated the transfer of learning effects from anti- to pro-reaching movements. The transfer was also 75%, supporting the predictions of 3) tuning-height modulation model.
We thus conclude that the switching rule affects height of tuning curve and partially diminishes motor learning effects even under the same planned movements.

Disclosures: **K. Takiyama:** None. **K. Ishii:** None. **T. Hayashi:** None.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

Location: Halls A-C

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Program#/Poster#: 694.12/LL28

Topic: E.04. Voluntary Movements

Support: Marquette University Committee on Research

Marquette University Strategic Innovation Fund

Title: Memory use during implicit learning varies across sensory feedback conditions, but is not impacted by interposed self-assessments

Authors: *R. SLICK[1], D. LANTAGNE[1], L. A. MROTEK[1,2], S. BEARDSLEY[1], D. THOMAS[3], D. LEIGH[1], I. AHAMED[1], R. A. SCHEIDT[1,4]
[1]Marquette Univ., Milwaukee, WI; [2]Univ. of Wisconsin Oshkosh, Oshkosh, WI; [3]Med. Col. of Wisconsin, Milwaukee, WI; [4]Northwestern Univ., Chicago, IL

Abstract: We examined error-based motor adaptation during practice of goal-directed reaching against unpredictable spring-like loads to quantify the impact of explicit recall of performance memories on implicit learning. Twenty human subjects sat in a high-backed chair and grasped the handle of a horizontal planar robot. An opaque horizontal screen occluded vision of the arm served as a display surface upon which visual stimuli were projected. All subjects participated in an initial "Performance Self-Assessment" testing session. Five subjects completed a secondary control session (the "Sensory Feedback Contrast" session). During the Self-Assessment session, subjects performed 3 blocks of 120 quick “out-and-back” reversal movements to capture a visual target mid-movement. The stiffness of the robot’s physical spring constant changed pseudorandomly from trial-to-trial. One of 3 conditions was tested per block, (*Proprioceptive Assessment (P), Visual Assessment (V), and* the *Control Condition(C)).* During *C*, all subjects completed the reach task without self-assessment. During the *P* trial block, subjects indicated their perceived reach extent by moving the robot handle - without load - to that location. During the *V* block, subjects indicated their perceived reach extent using a visual cursor controlled by a button box manipulated with the non-moving hand. During the Sensory Feedback session, five subjects returned to complete a block of *P trials* as well as a block of *VP* trials wherein the subjects had visual feedback via a visual cursor that tracked the hand faithfully. *Test Trials* included no visual feedback except during the *VP* block. In the Feedback Session, we found a significant influence of feedback condition such that ongoing visual feedback allowed for a reduced impact of past performance errors on future performances. Across conditions in the Assessment session, we found no difference in performance across conditions and no difference in how memories of past performances were used to update subsequent motor commands. Interposing explicit self-assessments between each trial had minimal impact on kinematic performance and error-based motor adaptation during reaching, despite the P trial block requiring active movement of the unloaded test arm in-between successive trials. Self-assessment of task performance does not appear to interfere with how the goal-directed reach was learned and performed; These two phases of the assessment trials may be interpreted by the CNS as distinct tasks. Support: Marquette University Strategic Innovation Fund.

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Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 694.13/LL29

Topic: E.04. Voluntary Movements

Title: The extent of overlap between explicit and implicit visuomotor learning

Authors: S. BAO[1], G. TAYS[2], *J. WANG[3]
[1]Univ. of Wisconsin Milwaukee, Milwaukee, WI; [2]Univ. of Wisconsin - Milwaukee, Milwaukee, WI; [3]Dept Kinesiology, Univ. of Wisconsin, Milwaukee, WI

Abstract: Adapting to a novel visuomotor condition during targeted reaching movements, a type of motor learning, has been traditionally thought to mainly involve implicit, as opposed to explicit, processes. This view was challenged by recent findings, which suggest that explicit processes may play a more significant role than previously thought. The objective of this study was to determine the extent to which visuomotor adaptation involves implicit and explicit processes, by investigating the pattern of transfer between two experimental conditions: one in which subjects dealt with a rotated visual display by relying on a cognitive strategy (explicit learning) and the other in which subjects dealt with the rotated display without being aware of it (implicit learning). It was hypothesized that if the typical visuomotor adaptation involved both explicit and implicit processes, substantial transfer would be observed between the two conditions. Healthy, right-handed young adults were separated into 2 groups: Implicit-to-Explicit, or Explicit-to-Implicit. Subjects in the former group experienced familiarization, implicit learning, and explicit learning sessions; and those in the latter group experienced familiarization, explicit learning, and implicit learning sessions. All subjects used the right arm in all sessions. During the explicit session, subjects were told to reach toward a position that was rotated 30º CW relative to one of 6 targets presented in a random order; and veridical visual feedback of a cursor indicating the hand position was provided throughout the movement. During the implicit session, subjects were told to reach toward one of 6 targets presented; and visual feedback of the cursor was rotated 30º CCW about the start position. Our results indicate that initial explicit learning did not facilitate subsequent implicit learning; and initial implicit learning did not facilitate subsequent explicit learning either. These results suggest that the extent of overlap between the cognitive and/or neural processes underlying implicit and explicit learning conditions is minimal, which in turn suggests that explicit processes may not play a very significant role in typical visuomotor adaptation.

Disclosures: S. Bao: None. **G. Tays:** None. **J. Wang:** None.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

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Program#/Poster#: 694.14/LL30

Topic: E.04. Voluntary Movements

Support: NIH Grant AG041878-05

Title: Implicit visuomotor adaptation has temporally stable and labile components, but explicit adaptation is entirely stable

Authors: *J. R. MOREHEAD[1], M. A. SMITH[2]
[1]Sch. of Engin. and Applied Sci., [2]Sch. Engin., Harvard Univ., Cambridge, MA

Abstract: Memories acquired through sensorimotor adaptation show partial decay over short intervals of time, from seconds to minutes (Sing et al., 2009). Recent work suggests that this is decay of an implicit memory, rather than an explicit strategy, but this observation was limited by experimental conditions that were not specifically designed to assess the time course of the memory decay (Miyamoto et al., 2014). Here we carefully measured the temporal decay curve of a visuomotor memory at multiple time points for both implicit and strategic learning (n=17). Participants were first trained to asymptotic performance with a 30° visuomotor rotation over 200 trials, while reaching to a single target. After this initial learning phase, we exposed participants to 7 different inter-trial time delays ranging from 3s to 90s in a randomized order. Each time delay was tested 8 times, with 9 readaptation trials between each exposure, allowing full asymptotic adaptation to be recovered before the next delay was imposed. Over this set of inter-trial delays, we observed a decay of the adapted state which rapidly increased in magnitude over short intervals of 3-10 seconds, before settling to a similar sized decrease for delays of 30-90 seconds. This change in behavior was consistent with an exponential decay of the adapted state with a time constant of approximately 13 seconds. The longest inter-trial interval we tested, 90 seconds, resulted in a decay of approximately 19% [95% CIs, -27%, -12%] of the asymptotic adapted state. We observed no change [95% CIs, -6%, 3%] in explicit aiming over any of the delay intervals, indicating that the temporally labile component of adaptation is implicit in nature. Moreover, upon repeating this experiment with a smaller 15° rotation (n=13), we measured a similar 16% [95% CIs, -26%, -6%] decay of the adapted state at the maximal inter-trial interval of 90 seconds, also with no change in explicit aim [95% CIs, -5%, 2%]. Our results suggest that for visuomotor rotation learning, approximately 15-20% of implicit adaptation decays over time. This is in contrast to explicit learning, which shows no appreciable decay over this time scale. Our findings show that explicit strategies are temporally stable, whereas implicit sensorimotor adaptation has both temporally-labile and temporally-stable components. Thus the temporally-labile component of motor adaptation is implicit in origin, whereas temporally-stable learning can arise from either implicit or explicit sources.

Disclosures: J.R. Morehead: None. **M.A. Smith:** None.

Poster

694. Human Motor Learning: Cognitive and Proprioceptive Influences

Location: Halls A-C

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Topic: E.04. Voluntary Movements

Support: NIH Grant 255-6655 (1R01NS084948-01).

Title: Sensitivity of implicit motor adaptation and explicit aiming

Authors: *S. A. HUTTER, J. A. TAYLOR
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Abstract: It has become increasingly clear that learning in visuomotor rotation tasks, which induce an angular mismatch between movements of the hand and visual feedback, largely results from the combined effort of two distinct processes: implicit motor adaptation and explicit aiming. However, it remains unclear how these two processes work together to produce trial-by-trial learning. Previous work has found that implicit motor adaptation is only sensitive to small errors and operates automatically, regardless of task relevancy and the actual effect of adaptation on performance. In contrast, little is known about the sensitivity of explicit aiming to visual errors and how it is affected by task relevancy. Here we sought to characterize the sensitivity function of these two processes and how they work together to facilitate performance in a visuomotor rotation task.

To test the sensitivity of implicit adaptation and explicit aiming to visual error, participants made reaching movements while experiencing pseudo-random perturbations of visual feedback. The relevancy of these errors to learning was manipulated by varying the number of trials in a row in which the same visual error (i.e., rotation direction and magnitude) and training location (i.e., target location) were experienced. Intended aiming direction was recorded via a touch screen before every movement and implicit adaptation was inferred by subtracting the aiming direction from the hand location.

We found that overall learning, as measured by hand angle relative to target, scales proportionally to the size of the visual perturbation. Implicit adaptation also scales relative to the visual error, but only for small perturbations (replicating Wei & Kording 2009). In contrast, explicit aiming does not play a role until visual errors are relatively large and/or implicit adaptation saturates. Furthermore, participants choose not to aim when the visual errors are task irrelevant, while implicit adaptation occurs even when visual errors are irrelevant to task performance. Although overall learning is proportional when errors are task relevant, this proportionality is accomplished through the combined effects of two separate and non-proportional components.

Disclosures: S.A. Hutter: None. **J.A. Taylor:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

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Topic: F.05. Neuroimmunology

Support: 5RC1DA028153-02

Title: CXCR4 but not CCR5 antagonism reduce the rewarding effects of the 'bath salt' 3,4-methylenedioxy-N-methylcathinone (MDPV)

Authors: *C. F. OLIVER[1], J. K. KIM[3], S. U. NAYAK[2], S. M. RAWLS[2]
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Abstract: Psychostimulant abuse is a major public health concern, yet there are no FDA-approved therapies available. 3,4-methylenedioxy-N-methylcathinone (MDPV) is a type of ‘bath salt’ that is ten times more potent but mechanistically similar to cocaine. This psychostimulant has powerful reinforcing effects that manifest as escalating self-administration and relapse following abstinence. Chemokines, leukocyte attractant inflammatory proteins, are dysregulated in cocaine users. Specifically, the receptor-ligand pairs CCR5-CCL5 and CXCR4-CXCL12 have been linked to cocaine use in humans and animals. We have found that AMD3100, a CXCR4 antagonist, decreased cocaine and MDPV-induced hyperlocomotion, self-administration, and conditioned place preference. We also found that maraviroc, a CCR5 antagonist, decreased MDPV-induced hyperlocomotion but not MDPV-induced conditioned place preference. Therefore the rewarding effects of MDPV and cocaine appear to be driven by a CXCR4-dependent mechanism. The results of these studies suggest that the FDA-approved chemokine antagonist AMD3100 but not maraviroc can attenuate the rewarding effects of MDPV and cocaine, making it an ideal candidate therapeutic for addiction to MDPV and other psychostimulants.

Disclosures: C.F. Oliver: None. **J.K. Kim:** None. **S.U. Nayak:** None. **S.M. Rawls:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.02/LL33

Topic: F.05. Neuroimmunology

Title: Profiling the neuroimmune response to poly I:C: sex differences, sickness behaviors, and memory

Authors: *C. K. POSILLICO, N. C. TRONSON
Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Aberrant neuroinflammation disrupts normal neural processes including learning and memory. Memory-related disorders such as Alzheimer's Disease and post-traumatic stress disorder have been linked with increased inflammation and have a higher prevalence in women compared with men. The bacterial endotoxin lipopolysaccharide (LPS) has been widely used to elicit robust immune activation via binding to toll-like receptor (TLR) 4 expressed on microglia. We have previously shown significant sex differences in acute hippocampal cytokine response to systemic LPS. However, it is important to consider how other physiologically relevant stimuli affect the neuroimmune system, particularly with respect to sex differences in the disruption of memory processes, as many immune responses involve mechanisms outside of the TLR 4 pathway. Thus, our study aimed to characterize the effects of acute polyinosinic:polycytidylic acid (poly I:C) on sickness behaviors, hippocampal-dependent memory tasks, and the neuroimmune profile of cytokines in male and female mice. Poly I:C is a viral mimic of double-stranded RNA that binds to toll-like receptor 3 expressed on astrocytes, microglia, and neurons, making it a useful tool to study the effects of broad-based inflammation on neuroimmune function and behavior. We administered an acute, intraperitoneal injection of poly I:C (6mg/kg and 12mg/kg), or its vehicle PBS, to both sexes to determine a time course and dose-response curve of sickness behaviors and fever response following peripheral immune activation. Next, we profiled the acute cytokine response of the hippocampus in response to peripheral poly I:C to determine how systemic immune activation affects a brain region crucial for memory formation. Finally, we examined the consequences of poly I:C on the induction and consolidation of distinct memories using contextual fear conditioning, novel object recognition and novel object location tasks. These findings will provide a broader understanding of the effects of a peripheral immune challenge on acute neuroimmune activation and its impact on memory, which will better inform research on memory disorders linked with a history of inflammation.

Disclosures: C.K. Posillico: None. **N.C. Tronson:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.03/MM1

Topic: F.05. Neuroimmunology

Title: The effects of a ketogenic diet on two-way active avoidance learning during an immune challenge in mice

Authors: E. GUENDNER, M. E. GIEDRAITIS, *R. A. KOHMAN
Psychology, Univ. of North Carolina Wilmington, Wilmington, NC

Abstract: Administration of the bacterial endotoxin lipopolysaccharide (LPS) leads to an inflammatory response that has been shown to disrupt learning and memory processes. One factor that can be utilized to potentially reduce inflammation is diet. The ketogenic diet (KD) is a high fat low carbohydrate diet that has shown some utility in reducing inflammation. Though the findings are mixed, there is also some indication that consuming a KD may have beneficial effects on cognitive function. Whether KD can attenuate inflammation-induced deficits in cognitive function has yet to be directly tested. Therefore the current experiment examined the effect of KD on the cognition of subjects exposed to LPS and tested in the associative learning task two-way active avoidance conditioning. In this task, subjects can learn to avoid or escape the presentation of an aversive stimulus. Previous research indicates that LPS given prior to training impairs performance in the task. The present experiment found modest deficits in avoidance learning in the LPS-treated mice as shown by reductions in response efficiency during later days of testing. The behavioral alterations induced by LPS administration were similar in mice fed the KD or control diet (CD). Additional work is currently in progress to determine whether KD modulates LPS-induced increases in cytokine levels. The KD mice showed improved performed compared to the CD mice in the two-way active avoidance task. While the results found no indication that KD attenuates LPS-induced behavioral deficits, they illustrate that KD itself may have beneficial effects on associative learning.

Disclosures: E. Guendner: None. **M.E. Giedraitis:** None. **R.A. Kohman:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.04/MM2

Topic: F.05. Neuroimmunology

Support: Groff Foundation

Title: Maternal high fructose diet and neonatal immune challenge alters offspring anxiety-like behavior across the lifespan

Authors: S. H. F. BUKHARI[1], O. E. CLARK[1], *L. L. WILLIAMSON[2]
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Abstract: Maternal diet has a profound impact on fetal and neonatal development, especially as obesity rates are on the rise worldwide. Specific macronutrient overabundance has been explored in some models of gestational diabetes, but the role of high fructose in the maternal diet

combined with a neonatal immune challenge remains unexplored in animal models. To test the interactions between *in utero* inflammation caused by maternal diet and neonatal inflammation caused by lipopolysaccharide (LPS), we bred 2 cohorts of dams, half fed with high fructose diet (60% fructose as carbohydrate source by weight) and half with normal chow (Teklad Diets). In the first cohort, each pup in a litter was injected subcutaneously on postnatal (P) 3 and P5 with either endotoxin-free 0.9% saline or 50ug/kg LPS. All pups in a litter were treated identically. On P7, 1 male and 1 female from each litter were tested for ultrasonic vocalizations (USVs) after a 10 min separation from the dam, as a measure of anxiety-like behavior. Subsequently, brain tissue was harvested and post-fixed in 4% formaldehyde. The remaining littermates were allowed to grow undisturbed until weaning and then undisturbed into adulthood. The adult offspring (P150-P200) were tested on the elevated zero maze (EZM) for anxiety-like behavior and in a context-object discrimination (COD) task for context memory. In a second cohort, neonates were treated with saline or LPS on P3 and P5 and all pups were weaned on P25. On P26, they were tested on the EZM and tested on the COD task on P32-34 prior to tissue harvest. While USVs showed no differences between maternal diet groups, neonatal treatment or sex, maternal diet and neonatal treatment had significant effects on juvenile (P26) behavior on the EZM. Offspring exposed to maternal high fructose diet spent significantly more time in the closed arms of the apparatus and offspring injected with saline spent significantly more time in the closed arms, with both effects likely driven by the offspring exposed to maternal high fructose and saline. In adults, offspring exposed to maternal high fructose diet spent significantly less time in the closed arms compared to offspring exposed to maternal normal diet. Surprisingly, neonatal LPS has an anxiolytic effect on the EZM in juveniles. However in adulthood, high fructose exposure also has an anxiolytic effect. Ongoing work will assess the results of COD testing and the cellular and molecular effects of maternal high fructose diet and its potential interactions with neonatal inflammation on the developing nervous system.

Disclosures: S.H.F. Bukhari: None. **O.E. Clark:** None. **L.L. Williamson:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.05/MM3

Topic: F.05. Neuroimmunology

Support: NIH grant MH100828

Title: Effects of intrauterine inflammation on cognition and motivation in male and female mice

Authors: *T. M. REYES[1], K. R. LLOYD[2], R. A. MAKINSON[2], H. LUNDE[2], S. K. YAGHOUBI[2]
[1]Psychiatry and Behavioral Neurosci., [2]Univ. of Cincinnati, Cincinnati, OH

Abstract: Chorioamnionitis, or intrauterine inflammation (IUI), occurs in approximately 10-15% of term births and is associated with developmental and psychiatric disorders including ADHD, autism, and anxiety disorders. We previously found that IUI in mice leads to white matter damage and increased novelty-seeking behavior in adulthood. Here, we hypothesize that IUI exposure will impair executive function. C57BL6/J female mice were bred to DBA males and then injected with lipopolysaccharide, a bacterial mimic, to induce a uterine-specific inflammatory response at embryonic day 15. The dams then delivered at term. Offspring were trained on operant behavior using an automated touchscreen apparatus beginning at 12 weeks of age, with males and females housed and tested in separate rooms. IUI offspring display hyperactivity during Pavlovian Conditioned Approach, with no changes to sign or goal tracking behavior. In a progressive ratio task, there was no effect of IUI on motivation in males, but female IUI mice were motivated to work for food reward than controls. Both sexes and treatment groups were able to learn a Fixed Ratio 1 (FR1) task, with prolonged training increasing the responses made by IUI females. There was no effect of sex or IUI status on performance in the 5 Choice Serial Reaction Time Task. The data suggest that IUI offspring display hyperactivity but maintain normal executive function abilities. In a related study, we found that male mice make comparable numbers of FR1 responses when housed in male-only or co-ed rooms, but females make more responses when housed in co-ed rooms. We hypothesize that the females, in response to male odor, are more motivated to work for food reward to acquire extra calories to support a potential pregnancy. These data highlight the importance of housing conditions during operant behavioral testing.

Disclosures: T.M. Reyes: None. **K.R. Lloyd:** None. **R.A. Makinson:** None. **H. Lunde:** None. **S.K. Yaghoubi:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.06/MM4

Topic: F.05. Neuroimmunology

Support: NIA Grant R15AG052935

Title: Assessment of associative learning in toll-like receptor-4 deficient mice

Authors: *O. V. POTTER[1,2], M. E. GIEDRAITIS[2], R. A. KOHMAN[2]
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Abstract: Toll-like receptor-4 (TLR-4) is a pattern recognition receptor that stimulates a proinflammatory innate immune response following detection of Gram-negative bacteria. Prior

research has established that stimulation of TLR-4 and the resulting inflammatory response produces transient cognitive deficits in a number of behavioral paradigms. Even in the absence of a TLR-4 agonist, TLR-4 has been shown to interfere with adult hippocampal neurogenesis and memory. However, the basal effects of TLR-4 on cognitive function are mixed; as TLR-4 deficient mice show enhanced spatial memory, impaired contextual and cued fear conditioning, and no differences in passive avoidance conditioning. To clarify these differential results, the current study compared TLR-4 deficient mice to control mice with functional TLR-4 receptors in an associative learning task. Adult male and female B6.B10ScN-Tlr4lps-del/JthJ (TLR-4-/-) and control C57BL/6J (TLR-4+/+) mice were assessed for alterations in locomotor behavior and anxiety-like behavior in the novel object exploration and open field tests. Subsequently, mice were evaluated in two variants of the two-way active avoidance conditioning task that differed in the time between trial presentation (i.e., inter-trial interval). Results showed that no differences in locomotor behavior or anxiety-like behavior exist between the TLR-4 deficient and control mice. Further, TLR-4 deficient mice showed comparable acquisition of the associative learning task relative to controls. Enhanced learning occurred in both strains with longer inter-trial intervals. Assessment of long-term retention of the avoidance task is currently in progress. Initial results indicate that the absence of TLR-4 has no negative effects on associative learning.

Disclosures: O.V. Potter: None. **M.E. Giedraitis:** None. **R.A. Kohman:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.07/MM5

Topic: F.05. Neuroimmunology

Support: NARSAD Young Investigator from the Brain & Behavior Research Foundation to JMS

Title: Examination into the effects of a second pregnancy on postpartum anhedonia and neuroimmune function

Authors: *J. GOMEZ[1], J. M. SCHWARZ[2]
[1]Dept. of Psychological and Brain Sci., Newark, DE; [2]Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: We have previously found that pregnancy (in first time mothers) produces significant anhedonia or depressive-like behavior immediately postpartum (Posilico and Schwarz, 2016). This anhedonia, as determined by a decrease in sucrose preference, is identical to that seen in female rats that are stressed for 1 week. We have also found that first time mothers have a striking increase in the pro-inflammatory cytokine IL-6 within both the medial prefrontal cortex

and the hippocampus, as well as a significant increase in Brain Derived Neurotrophic Factor (BDNF) within the medial prefrontal cortex all on the day of birth. These two brain regions are important for modulating mood and behavior, and have been implicated in many mood disorders, including depression. Similarly, elevated levels of circulating IL-6 have been associated with clinical depression in humans (Rich et al., 2017). This would suggest one of two things: either rats experience a short-lived postpartum anhedonia (resembling the "baby blues" described in humans) that is driven by an increase in IL-6 within the medial prefrontal cortex or the hippocampus; or the stress of a first-time pregnancy may be the cause of increased IL-6 within the brain and the associated postpartum anhedonia. We have begun to examine these hypotheses by studying postpartum sucrose preference and cytokine expression to see whether second pregnancies are also associated with these changes in neuroimmune function and mood. This research was supported by a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation to JMS.

Disclosures: J. Gomez: None. **J.M. Schwarz:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.08/MM6

Topic: F.05. Neuroimmunology

Support: MH104656

MH110415

Title: CCR6 mediates Th17 cells pathogenicity in depressive-like behavior in mice

Authors: *J. LOWELL, E. BEUREL
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Abstract: $CD4^+$ T-cells actively survey the brain and differentiate into effector T-helper (Th) cells in response to changes in the inflammatory milieu. Proinflammatory cytokines including interleukin (IL)-1β, TNFα, and IL-6 promote the differentiation of Th17 cells and have been found to be elevated in depressed patients. We previously found that Th17 cells promote susceptibility to depressive-like behaviors in mice, and accumulate in the brain of mice exhibiting depressive-like behavior. Furthermore, $ROR\gamma T^{+/GFP}$ mice that have impaired Th17 production show resilience to depressive-like behaviors. Together these indicate that Th17 cells have a pro-depressant effect. Here we show after transfer, Th17 cells infiltrate the hippocampal parenchyma in mice subjected to learned helplessness and identified the hippocampus and prefrontal cortex as two regions of accumulation. Unexpectedly, the majority of the Th17 cells

found in the hippocampus after transfer originated from the donor rather than the host, whereas $CD4^+$ T-cell transfer led to hippocampal accumulation of host $CD4^+$ T-cells. Furthermore, transfer of Th17 cells into $ROR\gamma T^{+/GFP}$ mice restored sensitivity to learned helplessness and led to increased GFP induction in the hippocampus. Together these findings suggest donor Th17 cells cooperate with the host immune system. To characterize Th17 cells infiltrating the hippocampus after learned helplessness, we analyzed 2 pathogenic surface markers, CCR6 and IL-23R and a T-follicular helper (T_{FH}), CXCR5. Th17 cells found in the hippocampus of learned helpless mice, compared to non-learned helpless mice, exhibit significantly increased expression of CXCR5, CCR6, and IL-23R, identifying T_{FH}17-like cells as potential arbiters of depressive-like behaviors. To assess the requirement of CCR6 in the pro-depressant action of Th17 cells, we transferred CCR6-deficient Th17 cells into wild-type mice and found CCR6-deficient Th17 cells unable to promote susceptibility to learned helplessness in contrast to wild-type Th17 cells. This revealed that CCR6 is required to induce Th17-dependent depressive-like behavior. Altogether, we have uncovered a subpopulation of Th17 cells that is associated with learned helplessness, which might provide a potential new avenue for characterizing biomarkers for depression.

Disclosures: **J. Lowell:** None. **E. Beurel:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

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Topic: F.05. Neuroimmunology

Support: Robert J. Stransky

Richard B. Fisher

Mary R. and Herman R. Charbonneau

College of the Holy Cross Summer Research Program

Title: Behavioral effects of maternal immune activation in mice

Authors: M. E. CRONIN[1], K. T. PRESTI[1], *A. C. BASU[2]
[2]Psychology, [1]Col. of the Holy Cross, Worcester, MA

Abstract: Epidemiological studies in humans have revealed associations between maternal immune activation during pregnancy and increased risk of schizophrenia in offspring. We sought to investigate the biological basis for this association by treating pregnant mice on gestational day 18 with the viral mimic polyinosinic:polycytidylic acid (poly I:C) and then assessing sensory gating, social behavior, and spatial cognition in adult male and female offspring. This study was

conducted in C57BL/6J mice (13 male and 11 female control offspring, 20 male and 11 female poly I:C exposed offspring). Data were analyzed using ANOVA, including treatment and sex as between-subjects variables, and an additional within-subjects variable as appropriate for repeated measures. Prepulse inhibition (PPI) of the acoustic startle response, a sensory gating phenomenon, was not affected by treatment or sex. The expected dependence of PPI on prepulse intensity was observed. There was a significant interaction between treatment and within-session trial block in our analysis of startle reactivity, suggestive of elevated initial startle response in female offspring of poly I:C treated dams. In the sociability assay, offspring of poly I:C treated dams were more sociable and demonstrated higher preference for social novelty than offspring of control (vehicle-injected) dams. Using a standard Morris water maze test of spatial learning and spatial reference memory, we found no significant effects of treatment or sex on path length, velocity or escape latency. We are currently conducting an analysis of spatial search strategies to further investigate the water maze results.

Disclosures: M.E. Cronin: None. **K.T. Presti:** None. **A.C. Basu:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

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Topic: F.05. Neuroimmunology

Support: NIH/NIAAA RO1 AA022460

R37 AA007789

NeuroDevNet (Canadian Networks of Centres of Excellence)

Canadian Foundation on Fetal Alcohol Research

Title: Impact of minocycline administration on neuroimmune outcomes following prenatal alcohol exposure

Authors: *T. S. BODNAR, J. WEINBERG
Cell. and Physiological Sci., The Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Prenatal alcohol exposure (PAE) has a significant impact on immune function, resulting in an increased risk of infections, alterations in immune organ development, and disturbances to immune cell populations. Importantly, altered immune function can impact both physical and mental health. Specifically, the neuroimmune system is involved in brain development, with perturbations linked to cognitive deficits and mental health disorders. We have shown previously that following PAE, cytokine levels are increased in the brain during the

early postnatal period, a critical window for both brain and immune system development. Based on these findings, here it was hypothesized that administration of an anti-inflammatory agent during early-life could have a beneficial impact on the neuroimmune system following PAE. To test this hypothesis, pregnant Sprague-Dawley rat dams were assigned to: PAE – *ad libitum* access to liquid ethanol diet; or Control (C) – *ad libitum* access to control diet. Next, male and female offspring were administered minocycline, an antibiotic that targets microglia. Minocycline was administered during either lactation [postnatal (P) days 1–15] or during adolescence (P33–43). Immune organs and brain tissue were collected during and following minocycline administration to assess cytokine levels. In adulthood, the response to lipopolysaccharide (LPS) challenge was assessed and, due to the modulatory role of the neuroimmune system on cognition and learning and memory, adult were tested in the Barnes Maze, an assessment of spatial learning/memory.
Results indicate that PAE increases thymus weight at birth and ongoing work is assessing whether this is associated with alteration in cytokine levels, as well as to assess the impact of minocycline administration. Immediately following lactational minocycline, levels of key immune cell were examined to confirm that minocycline does not have a suppressive effect on the developing peripheral immune system. Differences in lymphocyte, monocyte, basophil, and eosinophil levels were not detected following minocycline administration and thus minocycline does not appear to be negatively affecting the peripheral system. Ongoing work is evaluating whether minocycline administration impacts the response to LPS challenge as well as spatial learning/memory in the Barnes Maze.
Taken together, as altered immune function/neuroimmune signaling may underlie some of the long-term effects of PAE, findings from this ongoing study may have implications for understanding the long-lasting deficits associated with FASD and support further investment into immune-based intervention strategies.

Disclosures: **T.S. Bodnar:** None. **J. Weinberg:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.11/MM9

Topic: F.05. Neuroimmunology

Support: EDAPH105021

TCVGH-HK1048009

Title: The effects of alcohol on memory function and microglial cells in rat

Authors: *S.-Y. CHEN[1], C.-H. YANG[2], S.-N. YANG[2], J. WANG[1]
[1]HungKuang Univ., Shalu, Taiwan; [2]Departments of Pediatrics and Med. Research, E-DA Hospital, Col. of Medicine, I-Shou Univ., Kaohsiung, Taiwan

Abstract: Alcohol is the most widely consumed recreational drug. There are about 2 billion people as the regular consumers of alcohol in the world. It is known that alcohol is harmful to central nervous system (CNS). Evidence indicated that acute alcohol treatment induced marked functional impairments in learning and memory. Adult human reveal deficits in cognitive function such as working memory following consumption of alcohol. In normal condition, microglial cells are at a resting state in the brain. But alcohol as a neurotoxic factor that can activate microglial cells to release inflammatory mediators to induce further neuronal damage. However, the relationship between alcohol consumption and microglial dysfunction is not clear. In this study, we wanted to estimate the behavioral changes and the influence of microglia following alcohol exposure. Male SD rats fed with various concentration of alcohol for 1 week (Day 1 and 2: 1 %; Day 3 and 4: 5 %; Day 5, 6 and 7: 10 % alcohol). The diet of rats was restricted in order to decrease 20 % body weight. Then we started operating the behavioral experiment and estimated the memory functions by 8 arm maze. Rats were sacrificed after about 1 month. Our data indicated that the latency time of alcohol group was longer than control group. The memory task (total time) was significantly increased in alcohol group at Day 2, 3, 4 and 6 (291 ± 66 vs 791 ± 60; 465 ± 140 vs 852 ± 38; 409 ± 129 vs 724 ± 74; 376 ± 88 vs 791 ± 82 sec). The total working memory error (WME) and working reference error (WRE) were increased in alcohol group, too. The results of immunocytosatining of brain revealed that the activation of microglial cells increased significantly in prefrontal cortex and hippocampus (CA1). We suggested that alcohol will impair the normal memory function and induced the microglial cells activation.

Disclosures: S. Chen: None. **C. Yang:** None. **S. Yang:** None. **J. Wang:** None.

Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.12/MM10

Topic: F.05. Neuroimmunology

Title: The influence of social hierarchy on immune responsiveness

Authors: *D. AMADO RUIZ[1], T. LODDER[1], M. TOEBES[3], A. KALSBEEK[2], H. HU[4], T. N. SCHUMACHER[3], H. W. KESSELS[1]
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Netherlands; [4]Interdisciplinary Inst. of Neurosci. and Technology, Zhejiang Univ. Sch. of Med., Hangzhou, China

Abstract: Social status has been identified as one of the strongest predictors for human health. We used robust behavioral assays to measure the social hierarchy in groups of socially housed mice for which the hierarchy is established and stable, and violent acts of domination are largely absent. We found that the social status significantly correlated with the adaptive immune response in the periphery: mice with a high social status showed improved T-cell expansion upon antigenic stimulation. However, the brain regions that translate social status into improved immune responsiveness are unknown. The medial prefrontal cortex (mPFC) is known to play a central role in the control of social hierarchical behavior. To assess whether the mPFC also regulates immune function in the periphery, we manipulated synapse strength selectively at mPFC synapses by increasing or lowering AMPA-receptor levels at excitatory mPFC neurons. Our experiments demonstrate that enhancing AMPA-receptor levels at mPFC synapses is sufficient to improve antigen-specific T-cell responses. These experiments reveal a causal link between synapse strength in the mPFC, a brain area involved in higher order cognition, and the efficacy of the peripheral immune system.

Disclosures: D. Amado Ruiz: None. **T. Lodder:** None. **M. Toebes:** None. **A. Kalsbeek:** None. **H. Hu:** None. **T.N. Schumacher:** None. **H.W. Kessels:** None.

Poster

695. Neuroimmune Responses and Behavior

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Program#/Poster#: 695.13/MM11

Topic: F.05. Neuroimmunology

Support: NIDA Grant DA034721

NIDA Grant T32 DA07244

Title: Astrocyte specific mediation of heroin-conditioned immune suppression

Authors: *J. E. PANICCIA, C. L. LEBONVILLE, M. E. JONES, D. T. LYSLE
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Abstract: Exposure to both heroin and previously heroin-paired stimuli suppress peripheral indices of nitric oxide (NO) production, such as splenic inducible nitric oxide synthase (iNOS) and plasma nitrate/nitrite. Our laboratory has established the critical importance of interleukin-1β (IL-1β) signaling in the dorsal hippocampus (DH) for the expression of heroin-conditioned suppression of iNOS and nitrate/nitrite following re-exposure to the conditioned stimulus (CS). However, the cellular mechanisms of IL-1β remain unknown. The current set of experiments

investigated cell type specific expression of IL-1β during CS re-exposure, and manipulated cell type specific signaling *in vivo* in two different heroin-conditioning paradigms. In experiment 1, male rats underwent five conditioning sessions where heroin (1 mg/kg s.c) was paired with a distinct context for 1 hour every other day. Six days following the last session, animals were re-exposed to the CS, or remained in home cage as controls. Tissue was collected at three different time points: 30, 60, or 120 min following CS onset. Astrocytes were revealed as the cell type predominantly expressing IL-1β in our model. Thus, experiment 2 manipulated astrocytes *in vivo* using designer receptors exclusively activated by designer drugs (DREADDs) during CS re-exposure to disrupt heroin-conditioned immune suppression. We bilaterally infused GFAP-hM4Di-mCherry, a G_i-coupled DREADD under a GFAP promoter, into the DH of male rats. Following virus incubation, rats underwent heroin conditioning as outlined above. Six days later, animals were tested for the expression of heroin-conditioned immune suppression, and were either re-exposed to the CS, or remained in home cage. Clozapine-*N*-oxide (CNO; 3 mg/kg), or vehicle, was given 30 min prior to CS to activate the glial DREADDs. Immediately following CS, animals were given lipopolysaccharide (LPS; 1 mg/kg) to induce an immune response, and tissue was collected 6 hours later. Activation of GFAP-hM4Di-mCherry significantly attenuated heroin-conditioned suppression of plasma nitrate/nitrite and splenic iNOS mRNA expression. Experiment 3 investigated if the effect of GFAP-hM4Di-mCherry also disrupted heroin-reward associated memories. We bilaterally infused the construct into the DH of male rats prior to training in heroin-conditioned place preference (CPP). CNO administration 30 min prior to testing for the expression of heroin-CPP did not alter preference for the heroin-paired chamber. This suggests a specific role for G_i signaling in astrocytes to disrupt heroin-conditioned immune suppression, but not heroin-conditioned reward associations.

Disclosures: **J.E. Paniccia:** None. **C.L. Lebonville:** None. **M.E. Jones:** None. **D.T. Lysle:** None.

Poster

695. Neuroimmune Responses and Behavior

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Topic: F.05. Neuroimmunology

Support: NIDA Grant DA034721

NIDA Grant T32 DA07244

NSF GRF DGE-1144081

Title: Role of ventral hippocampus in context-heroin conditioned immunosuppression

Authors: *C. LEBONVILLE[1], M. E. JONES[1], J. E. PANICCIA[1], R. A. FUCHS[2], D. T. LYSLE[1]
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Abstract: Similar to heroin itself, exposure to environmental contexts associated with the prior effects of heroin can produce immunosuppression through Pavlovian associative conditioning. Our laboratory has demonstrated that the functional integrity of the basolateral amygdala (BLA), nucleus accumbens shell (NAcS), and dorsal hippocampus (DH) is necessary for the expression of this conditioned immune response. However, it is unknown whether the ventral hippocampus (VH) plays a role in this phenomenon. We tested the hypothesis that the VH plays a role in heroin conditioned immunosuppression based on its connectivity with the BLA and NAcS and based on evidence that projections from the VH to the NAcS may play a role in drug-related behavior. To test this hypothesis, we bilaterally infused an adeno-associated viral vector carrying the sequence for the G_i-coupled designer receptor exclusively activated by a designer drug (DREADD), HM4Di, under a CAMKIIα promotor (AAV5-CAMKIIα-HA-HM4Di-IRES-mCitrine) into the VH of male rats. Two weeks later, heroin (1 mg/kg) was repeatedly paired with access to a distinct context. After training (30 min before the test session), rats received systemic injections of the DREADD agonist, clozapine-*N*-oxide (CNO; 3 mg/kg), or vehicle. At test, rats were then re-exposed to the heroin-paired context for 1 h (to induce conditioned immunosuppression) or remained in their home cages (control). Rats then received a systemic injection of lipopolysaccharide (LPS; 1 mg/kg) to trigger the expression of proinflammatory mediators. VH inactivation failed to alter the heroin-conditioned suppression of splenic iNOS and plasma nitrate/nitrite levels assessed 6 h later. Together with our previous findings, these results indicate a role for the DH, and not the VH, in heroin-conditioned immunomodulation in the spleen.

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Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 695.15/MM13

Topic: F.05. Neuroimmunology

Support: NIH Grant DA034721

Title: Neuroimmune signaling in stress-enhanced fear learning, an animal model of post-traumatic stress disorder

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Abstract: Neuroimmune signaling is important in learning and memory processes. Further, converging evidence suggests that neural immune interactions, including astrocyte activity, are altered following stress exposure. For example, our laboratory has shown that the severe stressor in stress-enhanced fear learning (SEFL), an animal model of PTSD, induces a time-dependent increase in interleukin-1β (IL-1β) protein and mRNA and that blocking IL-1 signaling prevents the development of SEFL. Here, we employed triple labeling fluorescence immunohistochemistry to determine the cellular source of IL-1β and recent advances in chemogenetic technology to begin to explore the role of astrocytes, a key immune cell type in the central nervous system, in stress-enhanced fear learning. We used glial DREADDs (designer receptors exclusively activated by designer drugs) to test whether Gq and/or G_i signaling specifically in hippocampal astrocytes influences the development of SEFL. In Experiment 1, rats were exposed to Context A of the typical SEFL paradigm (15 2mA scrambled foot shocks over 90 minutes on a 6 minute variable interval schedule) and sacrificed via transcardial perfusion 48 hours later. Brains were extracted and tissue was processed for immunohistochemistry with primary antibodies against IL-1β and cell type specific markers for astrocytes, GFAP, neurons, NeuN, and microglia, Iba-1. Alexa fluor -conjugated secondary antibodies were used for visualization. Confocal microscopy and Bitplane Imaris colocalization analyses revealed that 92% of hippocampal IL-1β is expressed by astrocytes, while only 3% and 5% of hippocampal IL-1β is expressed in microglia and neurons, respectively. In Experiment 2, rats were infused with *AAV8-GFAP-hm4di-mcherry* or *AAV5-GFAP-hm3dq-IRES*-mCitrine directly into the dorsal hippocampus (DH) and allowed three weeks to recover from surgery and for the virus to express. Rats were then exposed to the typical SEFL paradigm and administered Clozapine-n-oxide (CNO) (3 mg/kg, s.c.) immediately, 24h and 48h after removal from Context A. Interestingly, while activating astroglial G_i signaling significantly attenuated the development of SEFL, activating astroglial G_q signaling did not influence SEFL. In summary, Experiment 1 quantitatively showed that astrocytes are the predominant cellular source of stress-induced IL-1β in the DH. Strikingly, our preliminary data in Experiment 2 showed that activating astroglial Gi signaling, but not astroglial G_q signaling attenuated SEFL, a PTSD-like phenotype. Further studies in our laboratory are testing whether any effects of glial GPCR signaling occur through an IL-1β-dependent mechanism.

Disclosures: M.E. Jones: None. **J.E. Paniccia:** None. **C. Lebonville:** None. **D.T. Lysle:** None.

Poster

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Topic: F.05. Neuroimmunology

Support: NSERC Grant R2195A01

Title: Effects of adolescent exposure to the short-chain fatty acid, propionic acid, and lipopolysaccharide on adolescent and adult rat anxiety and sensorimotor gating

Authors: *D. WAH, M. KAVALIERS, K.-P. OSSENKOPP
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Abstract: Alterations in the gut-brain axis have been implicated in the development of Autism Spectrum Disorders (ASD). Children with ASD show elevated levels of *Firmicutes* and *Desulfovibrio* bacteria in their stool. These bacteria produce short-chain fatty acids, such as propionic acid (PPA) and lipopolysaccharide (LPS) that affect anxiety-like behaviours and sensorimotor gating. The present study examined how an early adolescent exposure to LPS interacts with acute exposure to PPA in adolescence and adulthood on a measure of anxiety and sensorimotor gating. Adolescent male Long-Evans rats were administered 200 μg/kg LPS or vehicle intraperitoneally (i.p.) on postnatal days (P) 28, 30, 32, and 34. Rats were then injected with 500 mg/kg PPA or vehicle i.p. on P40 and tested on a Light-Dark (LD) task as an indicator for anxiety-like behaviour and locomotion. On P43, rats were again injected with 500 mg/kg PPA or vehicle i.p. and tested on Acoustic Startle Response (ASR) as an indicator of sensorimotor gating. In adulthood, rats were injected with PPA or vehicle and tested on P74 using the LD task and P77 using ASR. The results suggest that LPS interacted with PPA to decrease the number of light-dark transitions on the LD task in comparison to controls in adolescent rats. Finally, there were no differences in percent prepulse inhibition among treatments. Findings from this study will guide future research using an animal model of ASD through exposure to an immune insult and gut metabolite.

Disclosures: D. Wah: A. Employment/Salary (full or part-time):; University of Western Ontario. 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.; Natural Sciences and Engineering Research Council. **M. Kavaliers:** A. Employment/Salary (full or part-time):; University of Western Ontario. 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.; Natural Sciences and Engineering Research Council. **K. Ossenkopp:** A. Employment/Salary (full or

part-time):; University of Western Ontario. 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.; Natural Sciences and Engineering Research Council.

Poster

695. Neuroimmune Responses and Behavior

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Support: Samantha Alvarez-Herrera is a doctoral student from Programa de Doctorado en Ciencias Biomédicas, Universidad Nacional Autónoma de México (UNAM) and received fellowship 690152 from CONACYT

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Proyecto FT-IPN: IC-10-002

Title: Chemokine circulatory levels in adolescents MDD patients along eight weeks of clinical follow up with SSRI

Authors: *L. PAVON-ROMERO[1], F. DE LA PEÑA[3], C. CRUZ-FUENTES[4], M. I. GIRÓN-PEREZ[5], C. TELLEZ-SANTILLAN[6], S. ALVAREZ-HERRERA[2], G. PEREZ-SANCHEZ[2], E. BECERRIL VILLANUEVA[2]
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Abstract: Major Depression Disorder (MDD) is a global health emergency with 350 million people and 2-5.6% are adolescents; despite this, research on adolescents is limited. Regarding MDD, it has been reported that inflammatory response contributes to the onset of depression. In adults MDD patients, it has been described a link between the chemokine levels and the symptoms severity. We evaluated the serum levels of MCP-1(CCL2), MIP-1α(CCL3), MIP-1β(CCL4), IL-8(CXCL8), IP-10(CXCL10) and eotaxin(CCL11) in adolescents with MDD and their clinical psychiatric evolution by HDRS score. 18 healthy volunteers (HV) and 22 adolescents with MDD were evaluated along eight weeks (W) of clinical follow-up. In all cases, significant differences were detected in circulating chemokine levels between patients before treatment and HV ($P<0.0001$). Then, all chemokines evaluated showed a trend to decrease at

W4; however, only MCP-1 and IL-8 presented significant differences (P<0.05) between W0 vs W4. In adolescents with MDD, all chemokines rose to their initial concentrations (W0 vs. W8), but only IP-10 presented a significant (P<0.05) increase (W0 vs W8). All patients showed a significant decrease in their HDRS score at W4, (P<0.0001) and W8, (P<0.0001) compared to W0. Regarding the effect of fluoxetine on chemokine levels, our results showed a significant elevation of chemokines in adolescent with MDD despite the consumption of fluoxetine and improvement in HDRS scores. The high levels of eotaxin, IP-10 and IL-8 may partially explain some features of MDD as cognition, memory, and learning. Further studies are necessary to explore these findings and its implication in therapeutic approach.

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Poster

695. Neuroimmune Responses and Behavior

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Program#/Poster#: 695.18/MM16

Topic: F.05. Neuroimmunology

Support: NIMH Intramural Research Program, ZIA MH001090

Title: Elucidating adaptive roles for microglia in chronically stressed mice

Authors: *M. L. LEHMANN[1], T. K. WEIGEL[1], H. A. COOPER[2], S. L. KIGAR[1], M. A. HERKENHAM[1]
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Abstract: We hypothesized that chronic psychosocial stress can directly precipitate an immune reaction in the brain through activation of resident microglia and that the degrees and kinds of reaction are dependent on the psychological status of the animal. To model psychosocial stress in rodents, we used a chronic social defeat (CSD) paradigm. Mice susceptible to CSD (CSD-S) showed enduring deleterious behavioral consequences; however, a subset of resilient (CSD-R) animals avoided this outcome. We first performed a microarray analysis on microglia isolated from CSD-S and CSD-R mice to understand how these immune cells differentially respond to and perhaps contribute to stress adaptability. Gene expression profiles revealed that microglia from CSD-S relative to CSD-R mice might be phagocytically active and might promote a permeable blood brain barrier (BBB) that could support entry of peripheral monocytes into the brain. A series of *ex-vivo* and *in-vivo* experiments was performed to test the array results. First, microglia from CSD-S and CSD-R brains were isolated, placed in culture, exposed to fluorescently labeled apoptotic cells, and assayed for phagocytic activity. We found that

microglia from CSD-S mice compared to CSD-R mice contained higher levels of labeled debris and therefore were significantly more phagocytic. Second, BBB permeability was quantified in brains of CSD-S and CSD-R mice using i.v.-injected sodium fluorescein and, in addition, histochemically visualized using i.v.-injected fixable FITC-dextran. We found that CSD-S brains had substantially increased BBB permeability compared to brains from CSD-R and non-stressed mice. Third, we tested monocyte extravasation by injecting mice previously exposed to two weeks of CSD with peripheral blood mononuclear cells (PBMC) isolated from ubiquitously expressed GFP (Ubc-GFP) reporter mice. Brains and spleen were examined for GFP-positive cells three days after Ubc-GFP transfer. Although spleens from all groups showed colonization of GFP-positive cells, neither flow cytometry nor immunohistochemistry showed the presence of GFP-positive cells in brain in any condition, suggesting that CSD does not cause extravasation of PBMCs into brain. Together these results demonstrate that CSD-S microglia are more phagocytic and secrete molecules that break down the BBB, though at the time point examined, peripheral cells do not enter the brain. We hypothesize that these collective activities represent a CNS-centric inflammatory state that contributes to the susceptible phenotype. Causal relationships between microglia phenotype and behavioral phenotype are under current investigation.

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Poster

695. Neuroimmune Responses and Behavior

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Topic: F.05. Neuroimmunology

Support: NIH R01NS073939

Title: T cells are necessary for resolution of inflammation-induced depression-like behavior via an IL-10 dependent pathway

Authors: *A. KAVELAARS, G. LAUMET, J. D. EDRALIN, R. DANTZER, C. J. J. HEIJNEN
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Abstract: Major depressive disorder (MDD) is one of the most common mental disorders worldwide. Accumulating evidence indicates a role of the innate immune system in the onset of depression. In patients with MDD have increased level of circulating inflammatory cytokines and blood T cell count and proliferative responses to mitogens are reduced in depressed patients compared to mentally healthy individuals. On the basis of rodent studies of inflammation-induced depression-like behavioral it is known that IDO1 activity is necessary for depression-

like behavior (O'Connor et al, Mol Psy, 2009; Kim et al, JCI, 2012). *Ido1* expression is upregulated by proinflammatory cytokines such as IFNγ, TNFα and IL-1β (O'Connor et al, J Neurosci 2009). T cells are key regulators of the immune response and recent evidence has shown that T cells are also essential for maintaining central nervous system homeostasis (Ellwardt, Trends Immunology, 2016). However, little is known about the role of T cells in inflammation-induced depression. In order to investigate the role of T cells in inflammation-induced depression, we compared C57Bl/6 WT and T cell-deficient ($Rag1^{-/-}$ and $Rag2^{-/-}$) mice. Inflammation-induced depression-like behavior was measured as increased immobility time in the forced swim test in response to lipopolysaccharide (LPS) or Complete Freund's adjuvant (CFA). In both models, the onset of depression was similar between WT and T cell deficient mice, but depression-like behavior was drastically prolonged in T cell deficient mice. This was associated with prolonged upregulation of *Ido1* in the brain. Reconstitution of T cell-deficient mice with CD3+ T cells normalized resolution of depression-like behavior and expression of brain *Ido1*. During the resolution, T cells accumulated in the meninges but did not penetrate the brain parenchyma. In the brain, the inflammation-induced increase in pro-inflammatory cytokines such as *Ifng*, *Tnf* and *Il1b* was T cell independent. In contrast, T cells were required for induction of IL-10 in the brain. Nasal administration of neutralizing anti-IL-10 antibody prolonged depression-like behavior, indicating that brain IL-10 signaling is required for resolution of depression-like behavior. Transfer of IL-10-deficient T cells to T cell deficient mice was sufficient to induce resolution of depression-like behavior, indicating that T cells were not the source of IL-10. In conclusion, we show for the first time that T cells are required for resolution of inflammation-induced depression-like behavior and to silence *Ido1* expression in the brain via an IL-10-dependent pathway.

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Poster

695. Neuroimmune Responses and Behavior

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Topic: F.05. Neuroimmunology

Support: VA O1BX003631

Title: Effects of (R, S) Ketamine and (2R, 6R) hydroxynorketamine on lipopolysaccharide-induced sickness symptoms and anhedonia

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MD; [4]Res. and Develop. Service, Dept. of Veterans Affairs, VA Maryland Hlth. Care Syst., Baltimore, MD

Abstract: (R, S) ketamine (KET) is recognized for its rapid-acting antidepressant properties in humans, as well as rodent models. Recent studies have shown that (2R, 6R) hydroxynorketamine (HNK), a metabolite of KET, reverses stress-induced anhedonia and behavioral despair. It has also been reported that pre-treatment with low-dose KET in an inflammation model blocks the typical manifestation of these behaviors after sickness symptoms have subsided, approximately 24 h after an immune challenge. Given the known anti-inflammatory properties of KET, the goal of this study was to compare the effects of KET and HNK on lipopolysaccharide (LPS)-induced sickness behaviors and consummatory anhedonia. C57Bl/6J male mice (9 weeks of age; 8 mice/group) were administered either KET, HNK (20 mg/kg, i.p.) or vehicle followed 1 h later by either LPS (1 mg/kg, i.p.) or vehicle. Weight, temperature and sickness scores were recorded 2, 6 and 24 hours post injection. Twenty-four hours after LPS administration all groups underwent a sucrose preference test. KET, but not HNK, significantly attenuated sickness behavior 2 h post injection; however, neither KET nor HNK had significant impacts on LPS-induced changes in weight or temperature. In contrast, LPS-induced anhedonia in the sucrose preference test was completely blocked by HNK, but only partially by KET. This study suggests that, at the dose utilized, KET has anti-inflammatory effects that occur independently of its metabolite HNK. Moreover, our results show that HNK can prevent inflammation-induced anhedonia. Future studies will be required to elucidate the antidepressant and anti-inflammatory mechanisms of KET, and the mechanism by which HNK prevents anhedonia.

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Poster

695. Neuroimmune Responses and Behavior

Location: Halls A-C

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Program#/Poster#: 695.21/MM19

Topic: F.04. Stress and the Brain

Support: NIH Grant R01-HL089850

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Title: An inflammatory pathway links dietary antioxidant levels and human gray matter morphology: Moderation by cardiorespiratory fitness

Authors: *R. L. LECKIE[1], D. C.-H. KUAN[2], P. J. GIANAROS[3]
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Abstract: Several health behaviors can predict brain atrophy and cognitive decline, including diet and physical activity (PA). Specifically, greater dietary consumption of antioxidants (derived from fruits, nuts, and vegetables) and greater PA and cardiorespiratory fitness (CRF) are associated with larger GM volumes, even in midlife. Similarly, both antioxidant-rich diets and high CRF levels are associated with lower systemic inflammation. In fact, evidence suggests that systemic inflammation may play a role in effects of diet and PA on tissue morphology. Yet, it is unknown if the associations of diet and CRF with GM volume are independent or if they interact to predict brain volume via systemic inflammation. Accordingly, we tested whether GM volume in healthy middle-aged adults was associated with circulating antioxidant levels, and whether this association was accounted for by inflammation and moderated by CRF. Participants were 137 midlife adults (49%male, aged 30-50 years, mean age 40.7(6.15)). Blood samples were assayed for antioxidants (beta-carotene, alpha-tocopherol, gamma-tocopherol, beta-cryptoxanthin, retinol) and systemic inflammation (interleukin-6, C-reactive protein). CRF was estimated by resting heart rate, sex, height, and weight, and self-reported physical activity from the Paffenbarger Inventory. T1 MRI images were segmented for values of GM volume for the whole brain, four lobes, and select subcortical structures. Using residuals from intracranial volume, greater inflammation was associated with lower GM volume, while greater CRF moderated the association of antioxidant levels and GM volume in the frontal and occipital lobes. The dietary influences of antioxidant consumption may depend on PA, which has implications for age-related brain tissue losses and possibly cognitive decline.

Disclosures: R.L. Leckie: None. **D.C. Kuan:** None. **P.J. Gianaros:** None.

Poster

695. Neuroimmune Responses and Behavior

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Topic: F.05. Neuroimmunology

Title: Mating and reward system activation increases the expression of CCR5 on T cells

Authors: *T. BEN-SHAANAN, M. SCHILLER, N. BOSHNAK, B. KORIN, H. AZULAY-DEBBY, A. ROLLS
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Abstract: Mating is a major driving force in evolution. From an immunological perspective, mating is considered risky because of the potential exposure to sexually-transmitted pathogens. Although connections between mating and immunity are expected, they are still largely unknown. Here we show that mating elevates the expression of the chemokine receptor CCR5 on blood circulating CD4 and CD8 T cells. CCR5 is especially relevant for sexually transmitted diseases as it is the main cellular entry mechanism of the HIV virus. We demonstrate that

exposing male mice to mating-associated cues, or direct activation of the brain's reward system, associated with mating behavior, were sufficient to induce the increase in CCR5 levels. This increase in CCR5 expression was mediated by noradrenaline and peripheral opioids activity. Taken together, these results demonstrate a connection between, mating, activation of the reward circuitry, and CCR5 expression on T cells. Given the central role of CCR5 in HIV infection, our data suggests a possible mechanism whereby mating-associated immune reactions play a role in the evolutionary host-pathogen arms race.

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Poster

695. Neuroimmune Responses and Behavior

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Program#/Poster#: 695.23/MM21

Topic: F.05. Neuroimmunology

Support: NIH grant RO1GM62508

Title: Isoforms of HMGB1 modulate pain response in animals and activate neuronal cells

Authors: *H. YANG, Q. ZENG, M. ADDORISIO, M. K. GUNASEKARAN, S. S. CHAVAN, K. J. TRACEY
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Abstract: Secreted by activated cells or passively released by damaged cells, extracellular high mobility group box 1 (HMGB1) is an inflammatory mediator in both sterile injury and infection. Emerging evidence revealed that the release of HMGB1 following nerve injury plays a central role in the pathogenesis of neuropathic pain (Calvo M, et al, Lancet Neurol 2012, Karatas H et al, Science 2013). HMGB1 can directly act on nociceptors to induce pain as well as priming enhanced pain. HMGB1 expresses three cysteine residues and their redox states determine the biological function of HMGB1. All three cysteine reduced (fully reduced) HMGB1 induces chemotactic responses; mild oxidation (disulfide) HMGB1 is cytokine-inducing and pro-inflammatory; and oxidation of all cysteine residues (sulfonyl) HMGB1 has no known immune function (Yang H et al, Mol Med 2015). But it is not clear on the role of these isoforms of HMGB1 in neuropathic pain. Here we aimed to elucidate the effects of isoforms of HMGB1 in neuropathic pain and neuronal activation. Mechanical nociceptive threshold response in hind paw was determined in rats subjected to injection of isoforms of HMGB1. Compared to vehicle (PBS) -injected controls, intraplantar administration of disulfide HMGB1 (at 0, 2, 12 or 20 μg per paw) evoked mechanical hyperalgesia in female Sprague-Dawley rats in a dose-dependent manner [threshold response (gm) of vehicle = 4.1 $\pm$ 0.4, 0.2 μg/paw = 3.8 $\pm$ 0.6; 12 μg/paw =

2.3* ± 0.2, 20 µg/paw = 1.9* ± 0.2, N=6 or 12 per group, *: P<0.05 *vs.* vehicle group]. In comparison, fully reduced HMGB1 had similar effects whereas sulfonyl HMGB1 did not (data not shown). Systemic administration of neutralizing anti-HMGB1 monoclonal antibodies (mAb) ameliorates these hyperalgesia effects induced by disulfide HMGB1 in rats [threshold response (gm) of normal = 4.9 ± 1, HMGB1 alone = 1.9 ± 0.3, HMGB1 + mAb = 3.3* ± 0.3. *: P<0.05 *vs.* HMGB1 alone). In sensory neuron-like F11 cells, administration of disulfide HMGB1 significantly increased intracellular calcium influx (3.7 ± 0.3-fold increase over basal) whereas sulfonyl HMGB1 did not. Similar findings were observed using primary rat dosal root ganglions, indicating that disulfide HMGB1 activates neuronal cells *in vitro.* Exposure to albumin did not activate calcium influx, and the addition of neutralizing anti-HMGB1 mAb inhibited these effects; showing the specificity of the responses. Taken together, these results suggest that the redox state of HMGB1 is a critical determinant in neuropathic pain and in neuronal sensory neuron activation, with significant implications for developing experimental strategies targeting HMGB1-dependent neuronal-inflammatory diseases.

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Poster

696. The Blood Brain Barrier in Health and Disease

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Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: New Jersey Commission on Spinal Cord Research

Title: Characterization of hedgehog-responsive cells in the adult mouse spinal cord

Authors: M. S. RALLO, *M. P. MATISE
Rutgers-RWJMS, Piscataway, NJ

Abstract: Introduction: Sonic hedgehog (Shh) signaling plays an important role in both neural development and adult CNS function. The mechanism of signaling involves binding of Shh to the Ptch1 receptor, thus relieving the inhibition on Smo and allowing for differential activation of Gli transcription factors (Gli1-3) which mediate target gene expression. Notably, *Gli1* itself is a positively regulated target of Shh signaling. In the adult CNS, Shh is critical for maintaining pools of neural stem cells in the subventricular and subgranular zones of the brain as well as astrocytes within discrete regions of the forebrain. However, the distribution and properties of Shh-responsive cells in the adult spinal cord is yet to be elucidated.
Materials/Methods: To characterize $Gli1^{+}$ cells in the adult spinal cord we used two mouse lines: (1) a tamoxifen-inducible *Gli1:CreERT2;Rosa26:eYFP* line which permits lineage tracing

of cells expressing Gli1 indicating that they have received Shh signaling, and (2) a *Gli1:lacZ* line in which cells actively receiving Shh signaling express β-galactosidase. Spinal cord sections from the *Gli1:CreERT2;Rosa26:eYFP* animals were analyzed by IHC using neuronal- and glial-specific antibodies and RNA-seq to establish the molecular profile of these cells. The morphology and localization of $Gli1^+$ cells were also examined. *Gli1:lacZ* animals were fed BrdU in their drinking water for four weeks before collection to label slowly-proliferating cells within the adult spinal cord.
Results: Cells expressing Gli1 ($Gli1^+$ cells) were found distributed throughout the grey matter of the spinal cord 7 days following tamoxifen administration. No $Gli1^+$ cells were found in the white matter or ependymal zone. $Gli1^+$ cells co-labeled with glial markers Sox9, GFAP, Olig2 but not with the neuronal marker NeuN or the oligodendrocyte-lineage markers NG2, APC-CC1, MBP, or the microglia marker IBA-1. The molecular profile of $Gli1^+$ cells remained the same 1 year following tamoxifen administration. In addition, the cells displayed a highly branched morphology and were found in apposition to PECAM-stained blood vessels. The results of the proliferation analysis showed no incorporation of BrdU into $Gli1^+$ cells.
Conclusion: Our data indicate that $Gli1^+$ cells in the adult spinal cord represent a molecularly distinct subset of protoplasmic astrocytes in the adult CNS, suggesting a unique function. Based on the juxtavascular localization of the cells it is likely that these astrocytes are important components of the neurovascular unit. Future experimentation will assess the functional role of these cells in the lesioned spinal cord.

Disclosures: M.S. Rallo: None. **M.P. Matise:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

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Program#/Poster#: 696.02/NN1

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NHRI-EX106-10412NC

Title: Isoflurane mitigates Evans blue dye extravasation caused by carbogen inhalation in mice and rats

Authors: K. LIAO[1,3], K.-S. POON[1,3], Y.-L. PAN[1], H.-L. WANG[1], K.-B. CHEN[1,3], Y.-C. LIU[1,3], *T. W. LAI[2,1,4]
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Abstract: Isoflurane protects the blood-brain barrier (BBB) against cerebral extravasation of the Evans blue dye (EBD), a commonly used serum protein tracer, in animals subjected to BBB disruption. As such, it has been implicated as a therapeutic agent that can prevent brain edema and damage caused by a number of brain insults, including focal ischemia and intracerebral hemorrhage. In a recent study, we reported that isoflurane protects against cerebral extravasation of EBD following ischemic stroke in large through induction of hypothermia (Liu *et al*., 2017 PLoS One). This finding raised the possibility that isoflurane protected against other causes of BBB disruption also through hypothermia. To test this hypothesis, we subjected mice and rats to carbogen inhalation, an inducer of BBB disruption, in the presence or absence of isoflurane whilst measuring their rectal temperature. In mice, carbogen inhalation on its own caused marked hypothermia, and under this condition, isoflurane had no additional effect on rectal temperature. Nevertheless, isoflurane strongly protected against carbogen-induced cerebral extravasation of EBD. In addition, when temperature was maintained at 37^{o}C by means of an automated heating pad, isoflurane remained protective against cerebral extravasation of EBD. In rats, isoflurane mildly exacerbated carbogen-induced hypothermia, but also protected against cerebral extravasation of EBD. In conclusion, isoflurane strongly protected against cerebral extravasation of EBD caused by carbogen inhalation in mice and rats, but unlike isoflurane-mediated protection against ischemic BBB disruption, the effect here could not be explained by anesthesia-induced hypothermia.

Disclosures: **K. Liao:** None. **K. Poon:** None. **Y. Pan:** None. **H. Wang:** None. **K. Chen:** None. **Y. Liu:** None. **T.W. Lai:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.03/NN2

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Research Council of Norway, grant #226696

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Letten Foundation

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Simula-UCSD-University of Oslo Research and PhD training (SUURPh) program

Title: Interstitial solute transport in 3D reconstructed neuropil: Diffusion predominates

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Abstract: Although lymph vessels were recently discovered in the meninges, it is still widely debated how waste products are removed from the brain. It has been proposed that brain waste clearance occurs by bulk flow of interstitial fluid through neuropil as well as along blood vessels (the “glymphatic” concept [1,2]). A prerequisite for such an advection is a reasonably high hydraulic permeability. If the gaps between brain cells are too narrow, the neuropil permeability will be low and bulk flow will not be permitted for physiological pressure gradients.
Estimates of the neuropil permeability based on fluid injections and pressure recordings have several caveats, and the reported values for permeability of neuropil in the literature has a wide range, typically from 720 nm^2 to 4000 nm^2. Here we estimate the permeability based on a computer simulation of flow in electron microscopic (EM) reconstructions with realistic extracellular volume fractions.
We simulated bulk flow in geometries from Kinney et al. [3]. The extracellular space was divided into sheets and tunnels. Sheets were defined as the extracellular space between two parallel membranes (typically 10 to 40 nm wide), whereas tunnels were defined as the extracellular space where three or more membranes meet (typically 40 to 80 nm wide). For two different geometries with the same extracellular volume fraction we found that the geometry with the largest tunnel volume fraction had a 36% higher permeability. However, even for larger extracellular volume fractions than what is reported for sleep and for geometries with a high tunnel volume fraction, the permeability was too small to allow for any substantial bulk flow at physiological hydrostatic pressure gradients.
We also found that the permeability was about two orders of magnitudes lower (~10 nm^2) than what is typically reported in the literature. Our simulation results suggest that even large molecule solutes are more easily cleared from the brain interstitium by diffusion than by advection. Thus, we conclude that diffusion within the interstitial space combined with advection along vessels is likely to substitute for the convection-based lymphatic drainage system in other organs.
[1] Xie et al. (2013). Sleep drives metabolite clearance from the adult brain. Science, 342(6156), 373-377.
[2] Iliff et al. (2012). A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β. Science Translational Medicine, 4(147).

[3] Kinney et al. (2012). Extracellular sheets and tunnels modulate glutamate diffusion in hippocampal neuropil. *The Journal of Comparative Neurology*, *521*(2), 448-464.

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Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.04/NN3

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSF Grant 1537008 (CMMI)

Title: Mixture theory based analysis of the glymphatic system

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Abstract: It is well known that the lymphatic system, which is involved in the removal of toxins throughout the body, is absent in the brain. Thus the solute clearance mechanism of the brain remains an active area of research. In this context, a 'glymphatic system' was proposed by Iliff, Nedergaard and co-workers[1]. They observed exchange of metabolites from extracelluar space to the main cerebrospinal fluid (CSF) compartment. The observed rates indicated a prominent convective component to the flow of metabolites. To explain this, they proposed a pathway (glymphatic system) by which CSF is drawn into paravascular space of penetrating arteries and finds its way into parenchymal extracellular space primarily through AQP4 channels on the endfeet of astrocytic projections surrounding blood vessels. The interstitial fluid (ISF) is collected into the para-venous spaces. The flow was claimed to be driven mainly by arterial pulsations. The advection is said to be strong enough to carry macromolecules, thus leading to brain-wide solute clearance. We consider realistically inspired models of brain parenchyma to investigate if such a solute clearance mechanism can actually exist from a physical point of view. Previous numerical studies have assumed brain tissue to be a rigid solid with CSF flow through the inter-cellular spaces. We model the brain as a poro- elastic material and consider flow of CSF and passive transport of solutes. The Mixture Theory based Finite Element formulation developed by Costanzo and Miller[2] was used for numerical modelling of Fluid-Structure Interactions in the tissue. Here we discuss a relatively simple thought experiment: We check

whether a peristaltic wave traveling along arteries induces a significant convective flow of ISF in the surrounding tissue. This calculation is meant to ascertain whether or not pulsation alone in the absence of pressure gradients can in fact drive ISF convective flow. Our primary results show that such a scenario does not generate appreciable convective flow. Thus, if pulsation is the main driving element of the glymphatic system, it can only occur if mechanisms other than mere peristalsis are dominant.

[1] Iliff, J., Wang, M. and Liao, Y. et al. A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β. *Science Translational Medicine 4*, 147 (2012), 147ra111-147ra111.

[2] F. Costanzo and S. T. Miller. An Arbitrary Lagrangian-Eulerian Finite Element Formulation for a Poroelasticity Problem Stemming from Mixture Theory, Computer Methods in Applied Mechanics and Engineering (in print). Currently available at: http://arxiv.org/abs/1610.00079.

Disclosures: P.A. Patki: None. **B.J. Gluckman:** None. **P.J. Drew:** None. **F. Costanzo:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.05/NN4

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: CIHR Grant MOP119312

NIH Grant R01EB003268

Title: Treatment frequency of focused ultrasound mediated blood-brain barrier opening treatment for Alzheimer's disease

Authors: *C. POON[1], K. SHAH[2], R. TSE[1], K. KIM[1], S. MOONEY[1], K. HYNYNEN[1]
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Abstract: Background: Focused ultrasound (FUS)-mediated blood-brain barrier opening (BBBO) is a noninvasive method to enhance drug delivery to targeted regions of the brain. FUS BBBO has been used to deliver a variety of agents to the brain (e.g. chemotherapeutics, natural killer cells) and results in an increased rate of neurogenesis. Using FUS-mediated BBBO, antibodies directed against amyloid-β (Aβ) have been successfully delivered to the brain parenchyma of the TgCRND8 mouse model of AD. A follow-up study showed that three weekly treatments of FUS-mediated BBBO targeted to the bilateral hippocampus (without therapeutics) significantly decreased Aβ plaque load and improved spatial memory performance in AD mice to the levels of non-transgenic controls.

Objective: The objective of this study is to determine if five biweekly (once every two weeks) FUS-mediated BBBO treatments reduces Aβ plaque burden and improves cognitive functions in the TgCRND8 mouse model of AD, and to compare this with the results from the three weekly FUS treatments study [Burgess *et al.*, Radiology 2014].
Methods: Seven-month old TgCRND8 mice were given FUS-mediated BBBO treatments targeted to the bilateral hippocampi once every two weeks for a total of ten weeks. FUS treatments were conducted by mechanically scanning a spherically curved transducer (1.68 MHz, 10 ms bursts, 1 Hz burst repetition frequency, 120 s duration) in conjunction with a bolus injection of Definity microbubbles (20 μl/kg) under magnetic resonance imaging (MRI) guidance at 7T. Hippocampus-dependent memory was assessed using the Novel Arm Y-Maze test one week after the last FUS treatment. Bromodeoxyuridine (BrdU) was injected 2 hours before sacrifice. Aβ plaques were stained using immunohistochemistry, and quantified using stereology.
Results: Biweekly FUS treatments were well-tolerated by TgCRND8 mice. After five biweekly FUS treatments, plaque burden decreased significantly in AD FUS mice compared to AD control mice (413.7 ± 16.1 compared to 298.6 ± 24.1, mean ± SEM, n=5-8). Results were comparable to the three weekly FUS treatments regime [Burgess *et al.*, Radiology 2014].
Significance: Although FUS-mediated BBBO will likely be used as a means to deliver AD therapeutics in order to maximize treatment efficiency, the effects of the FUS itself on AD symptoms should be determined. The frequency of FUS treatments delivered to AD patients must be clinically feasible and result in maximal treatment benefits.

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Poster

696. The Blood Brain Barrier in Health and Disease

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Program#/Poster#: 696.06/NN5

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01NS078168

NIH Grant R01NS079737

Scholar Award from the McKnight Endowment Fund for Neuroscience

Title: Anatomical basis for cerebrospinal fluid transport through the cribriform plate in mice

Authors: *J. N. NORWOOD[1], D. CARD[2], A. CRAINE[3], T. RYAN[4], Q. ZHANG[5], P. J. DREW[5,6,3]

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Abstract: Cerebrospinal fluid (CSF) is thought to be transported into and out of the brain via the glymphatic system. Decreased turnover of CSF in the brain plays a role in aging and in neurodegenerative disorders. However, the anatomical pathways by which CSF and interstitial fluid (ISF) leave the brain are poorly understood, and elucidating these pathways is important as they will play a role in controlling CSF turnover. There is evidence that the CSF exits into the nasal epithelium via the cribriform plate, the perforated bone through which olfactory sensory neurons enter the brain. To better understand the anatomical substrate at the microscopic and mesoscopic scale, we used microCT imaging and histological reconstructions of the nasal turbinates, cribriform plate and olfactory bulbs in mice. CT imaging revealed the cribriform plate was highly porous, with four major foramina located laterally from the crista galli, the ridge of bone along the midline of the plate. Multiple, smaller foramina, lined with Aquaporin-1, concentrated mostly along the crista galli were also observed. Blood vessels were observed traversing foramina of the plate. Using cell-type specific labeling in transgenic mice, the relationship of the dura and lymphatic vessels along the olfactory nerves was investigated. We are currently examining the microscopic anatomy of the outflow pathway (interstitial space between nerves, blood vessels, and lymphatics) with injections of FITC-albumin. Our results show that the cribriform plate is an important CSF outflow pathway in mice.

Disclosures: J.N. Norwood: None. **D. Card:** None. **A. Craine:** None. **T. Ryan:** None. **Q. Zhang:** None. **P.J. Drew:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

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Program#/Poster#: 696.07/NN6

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: FRN 119312

R01 EB003268

Canada Research Chair Program

Title: Exploring the angiogenic response of hippocampal vasculature to focused ultrasound-mediated increases in blood-brain barrier permeability

Authors: *D. MCMAHON[1,2], K. HYNYNEN[2,1]
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Abstract: Therapeutic treatment options for central nervous system diseases are greatly limited by the blood brain barrier (BBB). Focused ultrasound (FUS), in conjunction with circulating microbubbles, can be used to induce a targeted and transient increase in BBB permeability, providing a unique approach for the delivery of drugs from the systemic circulation into the brain. While preclinical research has demonstrated the utility of FUS, there remains a gap in our knowledge regarding the long term response of brain vasculature. This work stems from a study demonstrating transcriptional changes in hippocampal rat microvessels in the acute stages following sonication. Microarray analysis of microvessels was performed at 6 and 24 hrs post-FUS and suggest that FUS may initiate angiogenic processes. Preliminary results suggest that these changes in gene expression manifest as increased perfused vessel density in CA1 at 9 days following sonication. The time course of this angiogenic response, from 7 days to 21 days, was also investigated with BrdU and GLUT1 colocalization and demonstrates increases in vessels density and newborn vascular endothelial cells in the sonicated regions. While further work is necessary, these results open up intriguing possibilities for novel FUS applications in neurological disorders in which vascular density is negatively affected.

Disclosures: D. McMahon: None. **K. Hynynen:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

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Program#/Poster#: 696.08/NN7

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: U54NS083924

8G12MD00758

8G12MD007600

Title: Nuclear functional kinin-B2 receptors in the human hCMEC/D3 blood brain barrier cell model

Authors: *M. N. GONZALEZ VEGA[1], Y. FERRER ACOSTA[2], W. TORRES[3], A. H. MARTINS[4]
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Abstract: Bradykinin (BK) is a nonapeptide which is generated by kininogen. BK acts through the kinin-B2 receptor (B2BKR), a G-coupled protein receptor that belongs to the kallikrein-kinin system and it is expressed in blood brain barrier (BBB) forming cells. The activation of the B2BKR increases the permeability of the BBB. There are cell models that mimic the BBB,

however the immortalized human cerebral microvascular endothelial cell line (hCMEC/D3) is well known since the cell line can form the BBB without the presence of other cells. Even though the role of B2BKR is important in the BBB, the expression or activity is yet unknown in hCMEC/D3. The role of this project was to determine the expression and effect of B2BKR on hCMEC/D3. Hence, the expression of B2BKR was assessed by western blot and the cellular localization by immunofluorescence followed by z-stack analysis. The functionality of B2BKR was measured by calcium imaging and patch-clamp recordings. Whole cell lysate demonstrated the presence of B2BKR on hCMEC/D3, however extracellular stimulation with bradykinin did not induce any change in intracellular calcium release. The localization of B2BKR was detected in the nucleus of hCMEC/D3 cells using immunofluorescence with anti-B2BKR and a z-stack analysis. To determine if the intracellular B2BKR was functional, the activity was observed using patch-clamp recordings. Measurements of the inward calcium currents made before and after intracellular administration of the peptide to the pipette solution, revealed a decline of inward calcium current supporting the view that BK has an intracrine effect in hCMEC/D3 cells. The findings demonstrated that hCMEC/D3 cells express functional B2BKR in the nucleus, providing new mechanistic insights into B2BKR functioning in these cells highly used to mimic the BBB.

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Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

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Program#/Poster#: 696.09/DP10/NN8 (Dynamic Poster)

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Sanofi funding

Title: Aberrant Cdk5 activation induces blood-brain barrier modifications in CK-p25 mice, an inducible model of neurodegeneration

Authors: *C. TACCOLA[1], S. CARTOT-COTTON[2], D. VALENTE[3], P. BARNEOUD[4], M. LOCHUS[1], X. DECLÈVES[1], F. BOURASSET[1]
[1]Lab. de Pharmacocinétique, Faculté De Pharmacie, Inserm UMR-S 1144, Paris, France; [2]Pharmacokinetics, Dynamics and Metabolism, [3]Drug Metabolism and Pharmacokinetics, Res. Platform, [4]Neurosci. Therapeut. Area, Sanofi, Paris, France

Abstract: Drugs aimed at treating central nervous system disorders need to cross the cerebral endothelium, also known as the blood-brain barrier (BBB). The BBB is a dynamic interface modulating exchanges of compounds between the brain and blood and plays a crucial role in

maintaining brain homeostasis. Modifications of the BBB have been shown in Alzheimer's disease (AD) patients and in various AD mouse models. Prolonged and aberrant p25-dependant Cdk5 activation has been linked to neurotoxicity and several neurodegenerative disorders including AD. CK-p25 is a transgenic mouse model of neurodegeneration (ND) that inducibly overexpress the human p25 protein. To date, little is known on the BBB integrity of these mice. We used the *in situ* brain perfusion method to investigate the implications of Cdk5 aberrant activation on the physical and functional integrity of the BBB of these mice on early (3 weeks) and advance (6 weeks) stage of p25-induced ND. We first confirmed that p25 induction was accompanied by significant brain atrophy with a decrease in brain weight of 15 to 30% at early and advanced stage of ND respectively. The cerebrovascular volume of distribution of sucrose, a vascular space marker, was significantly increased in p25-induced mice from early stage of ND, suggesting an impaired BBB permeability, but without significant changes observed in the expression of tight junction proteins. The expression and function of cerebral essential nutriments and amino-acid transporters such as Glut-1 and LAT-1 were significantly increased on advanced stage of ND suggesting an adaptive compensatory mechanism for p25-induced neurotoxic insults. Most ABC-family efflux transporters were significantly increased on advanced stage of ND, probably in response to cerebral neurotoxic compounds accumulation. Finally, we showed that influx and efflux transporters of cholesterol and amyloid-β (Aβ) peptide, two compounds that play a critical role in AD pathology, were greatly modulated. In conclusion, CK-p25 mouse model is a valuable and fast model that could be of great interest in ND new therapy development. We showed that CK-p25 mice display an increased BBB permeability and profound functional modifications, some of which interestingly differ from those described in other AD or neurodegeneration mouse models. BBB damages could drastically impair cerebral homeostasis and thus neuronal and glial function. Many studies have already suggested that AD and cerebrovascular abnormalities are closely linked but it remains to be investigated if BBB dysfunctions are a cause or a consequence of the neurodegeneration.

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Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.10/NN9

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NRF

Title: Establishing multiple cell culture model of the blood-brain barrier

Authors: *M.-H. JO, N. B. ABID, M.-W. KIM, A. KHAN, M. KHAN, M.-O. KIM
Gyeongsang Natl. Univ., Jin-ju, Korea, Republic of

Abstract: Blood brain barrier a neurovascular complex which acts as a selective semi-permeable membrane separating circulating blood from brain extracellular fluids. BBB not only controls trafficking of material in and out of CNS but also regulates homeostasis of brain. For last decade BBB research have not only been highlighted to understand mechanisms of drug delivery but also to elaborate correlations between neurodegenerative diseases and BBB disruption. To attain detailed mechanisms at molecular level a comprehensive *in vitro* model is required which is capable enough to mimic physiological environment under control experimental conditions. In present study we established a multiple cells *in vitro* model of BBB comprises of brain endothelial cells (BEndo.3), astrocytes (astrocytes clone Type I) and neuronal cells (HT22). Model in present study is not only capable to provide structural and physiological details of neurovascular complex to study drug delivery but also addresses role of BBB integrity in neurological disorders (Alzheimer's disease, Parkinson's disease, etc.) and traumatic conditions (Traumatic brain injury, Ischemia etc.). Present study is a comprehensive mechanistic approach which covers *in vitro* and *in vivo* disease models. It will provide better understanding of neurological disorders and will provide an insight to design futuristic therapeutic strategies. (supported by NRF)

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Poster

696. The Blood Brain Barrier in Health and Disease

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Program#/Poster#: 696.11/NN10

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: AG039452

AG023084

NS034467

NS100459

Title: Pericyte degeneration leads to diffuse white matter disease

Authors: *A. MONTAGNE[1], A. M. NIKOLAKOPOULOU[1], Z. ZHAO[1], G. SI[1], A. P. SAGARE[1], D. LAZIC[1], S. R. BARNES[3], M. DAIANU[2], A. RAMANATHAN[1], A. GO[1], E. J. LAWSON[1], Y. WANG[1], W. J. MACK[1], P. M. THOMPSON[2], J. A. SCHNEIDER[4], R. E. JACOBS[1], B. V. ZLOKOVIC[1]
[1]USC, Los Angeles, CA; [2]Inst. for Neuroimaging and Informatics, USC, Marina Del Rey, CA; [3]Caltech, Pasadena, CA; [4]Rush Univ. Med. Ctr., Chicago, IL

Abstract: Diffuse white matter disease has been observed in many neurodegenerative diseases including small vessel disease and dementia. Pericytes are vascular mural cells embedded in the wall of the smallest blood vessels. In the brain, they control blood-brain barrier (BBB) integrity and cerebral blood flow (CBF) and they participate in clearance of toxins. Mice with global pericyte degeneration, caused by platelet-derived growth factor receptor-β (*Pdgfrβ*) deficiency in pericytes ($Pdgfr\beta^{F7/F7}$), have been shown to develop aberrant CBF responses and chronic BBB breakdown associated with brain accumulation of serum proteins in grey matter regions (e.g., cortical mantles and hippocampus). However, whether white matter is affected by pericyte loss, and whether pericytes are necessary for healthy white matter, remain unknown to date. Using $Pdgfr\beta^{F7/F7}$ pericyte-deficient mice, magnetic resonance imaging, viral-based tract-tracing, behavior and tissue analysis, we show that pericyte degeneration leads to early deposition of blood-derived neurotoxic products and blood flow reductions in the white matter causing diffuse white matter degeneration and loss of myelin, axons and oligodendrocytes. This disrupts brain circuits leading to white matter functional deficits long before neuronal loss occurs. Overall, our data suggest that pericytes are critical for proper white matter structure and functional connectivity, which has implications for the pathogenesis and treatment of human white matter disease and small vessel disease.

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Poster

696. The Blood Brain Barrier in Health and Disease

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Program#/Poster#: 696.12/NN11

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Chinese FRFCU 2016QN81017

Chinese NSF 61673346

Chinese NSF 81600982

Title: Evaluating the size of focused ultrasound-induced blood-brain barrier opening in cats using 7 Tesla magnetic resonance imaging

Authors: *H.-Y. LAI[1], X. FENG[1], C.-T. WANG[1], T. HE[1], W. XIONG[1], C.-H. TSAI[2], B. XU[1], H.-L. LIU[1,2]
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Abstract: Focused ultrasound with the presence of microbubbles has been shown to transiently open the blood-brain barrier (BBB) and brings new opportunity in delivering molecules into the brain. Our previous study demonstrated that 0.55-mechanical index (MI) FUS intensity is the safe range of exposure to induce BBB opening in rats. However, the optimum acoustic pressure of FUS-induced BBB opening may be different in large animals due to the skull. The purpose of this study is to evaluate safety and size of the BBB opening in cats using 7 Tesla Magnetic Resonance Imaging (MRI, Siemens 7T Magnetom) and Evans Blue (EB) dye at distinct acoustic pressures and exposure periods. We systematically presented 0.9- and 1.2-MI FUS with the intravenous injection of microbubbles for 15, 30, 60 and 120 s exposures in the cat brain. The T1-weighted images were recorded to assess the size of BBB opening before FUS, and 0.5, 1.5, 2.5, 3.5, 4.5, 5.5 and 6.5-h post-FUS. To localize the spatial distribution of BBB opening, EB dye (1 ml/kg) was injected intravenously immediately following FUS. To Noninvasively monitor the dynamic changes of the spatial distribution of FUS-induced BBB-opening, the whole brain 3D dynamic contrast-enhanced (3D-DCE) images were recorded for 5 min after each MRI

contrast-agent, Gadolinium-DTPA (Gd-DTPA, 0.3mmol/kg), IV injection at 0.5, 3.5, 6.5 h and 1 day post-FUS. After finish of all MRI recordings, all animals were deeply anesthetized with chloral hydrate (350 mg/kg) and sacrificed to get EB-stained brains. T1-weighted images showed that BBB could be disrupted by using 1.2-MI FUS for 30, 60, and 120 s, as well as 0.9-MI FUS for 60 and 120 s. The 3D-DCE images showed that BBB closed after 3.5 h and there is no BBB opening after 1 day post-FUS. The size of BBB opening is related to both acoustic pressures and exposure periods. The EB-stained brains showed the leakage region which was correlated with the results of 3D-DCE images. As compared with the rat, the safe acoustic pressure of FUS-induced BBB opening is higher because of the thickness and microstructure of skull. These results demonstrated that FUS-induced BBB-opening can be used successfully in cats, and it might potentially apply to the nonhuman primate and further clinical applications.

Disclosures: H. Lai: None. **X. Feng:** None. **C. Wang:** None. **T. He:** None. **W. Xiong:** None. **C. Tsai:** None. **B. Xu:** None. **H. Liu:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.13/NN12

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: University of Wisconsin-Madison School of Pharmacy

Michael J Fox Foundation for Parkinson's Research

UW Institute for Clinical and Translational Research (NIH UL1TR000427 and KL2TR000428)

Wisconsin Alumni Research Foundation

National Science Foundation fellowship (DGE-1256259)

Clinical Neuroengineering Training Program fellowship (NIH NRSA T32 EB011424)

Title: Intranasal delivery of antibodies achieves significantly higher CNS to blood ratios than systemic delivery - an investigation of distribution, pharmacokinetics, dose-response, and mechanism of transport

Authors: *N. KUMAR[1], J. J. LOCHHEAD[1], M. E. PIZZO[1], D. J. WOLAK[1], G. NEHRA[1], S. BOROUMAND[1], E. BRUNETTE[5], D. STANIMIROVIC[5], R. G. THORNE[1,2,3,4]
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Abstract: Intranasal delivery is a non-invasive strategy that can potentially bypass the blood-brain barrier (BBB) and blood-cerebrospinal fluid barriers (BCSFBs) to rapidly target biologics to the CNS via extracellular pathways (Thorne et al. *Neuroscience* 2004 & 2008; Lochhead et al. *J. Cereb. Blood Flow & Metab.* 2015). Here, we provide a detailed comparison of antibody delivery to the CNS following intranasal (IN) versus intra-arterial (IA) administration. Anesthetized rats were administered either radiolabeled or fluorophore-labeled antibodies. To investigate dose response following IN delivery, we compared a tracer dose (50 µg), a middle dose (1000 µg), and a high dose (2500 µg) of radiolabeled IgG in separate experiments. Higher IN doses resulted in greater CNS exposure, suggesting access to extracellular pathways to the CNS that are not easily saturated. Dose-response following IA delivery was first investigated for IgG doses that resulted in blood exposure similar to the IN doses at the experimental end-point (30 minutes following administration). IA delivery resulted in significantly lower CNS IgG levels compared to IN delivery for each matched dose. Next, we examined dose-response following IA delivery for IgG doses equal to the IN doses. IA delivery resulted in significantly higher blood exposure than IN delivery at 30 minutes following administration. However IgG delivery to the CNS did not scale up as dramatically following equal dose IA compared to IN delivery. Furthermore, we observed that following IA delivery of fluorophore-labeled IgG at a dose equal to IN delivery, the fluorescent signal was largely restricted to the endothelial compartment. Our studies involving IN delivery of fluorophore-labeled IgG provide the first evidence for a three step nose-to-brain delivery process for antibodies that bypasses the BBB via transport: 1) Across the nasal epithelium; 2) Along the perineural compartments of the olfactory and trigeminal nerves; 3) Within the brain along the perivascular space (PVS) of cerebral blood vessels. The PVS is a fluid-filled compartment; bulk flow and transport in this compartment is likely to scale with brain size across different species (Wolak & Thorne. Mol. Pharma. 2013). The ability of IN delivered IgG to access the PVS compartment is therefore highly relevant for potential clinical translation. Finally, we have recently reported relatively low vascularity and vascular permeability in the nasal olfactory region, suggesting IN targeting of drugs to that area may favor brain delivery due to reduced clearance to the systemic circulation (Kumar et al. *Sci. Rep.* 2016).

Disclosures: **N. Kumar:** None. **J.J. Lochhead:** None. **M.E. Pizzo:** None. **D.J. Wolak:** None. **G. Nehra:** None. **S. Boroumand:** None. **E. Brunette:** None. **D. Stanimirovic:** None. **R.G. Thorne:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.14/NN13

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: G12MD007600

1U54NS083924-03

Title: NG291 a stable B2 kinin receptor agonist increase the permeability in normal blood brain barrier- possible role in organophosphate poisoning

Authors: S. R. MASSO[1], S. MARTINEZ[2], V. A. ETEROVIC[3], P. A. FERCHMIN[4], *A. H. MARTINS[1]
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Abstract: Organophosphates are phosphorus-containing compounds that inhibit the acetylcholinesterase generating a cholinergic crisis that is fatal if not treated. The classical antidote atropine and pralidoxime are able to protect peripherally, but cannot protect the central nervous system. Pralidoxime is the only FDA approved drug that re-activates the inhibited acetylcholinesterase by organophosphate. Pralidoxime has limited neuroprotective potential because it is not able to cross the blood brain barrier (BBB) effectively. In order to increase this potential, our group is using a stable B2 kinin agonist NG291. This peptide can transiently open the BBB and increase the pralidoxime delivery to the brain after organophosphate poisoning. Sprague-Dawley rats were subjected to NG291 treatment (50µg/Kg) via intravenous (IV) route followed by 2% Evans Blue dye injection. 24 hours after the peptide injection the animals were perfused and the amount of albumin-Evans blue was qualitative analyzed. To verify whether the transient opening of the BBB increased brain water content, 11 controls (saline) and 12 rats injected with the peptide NG291 were euthanized 24 hours after the peptide injection, and the percentage of water content was measured. To assure that the transient opening of BBB does not cause brain damage, control and NG291 injected rodents were stained with Fluoro-Jade C to verify the presence of dead neurons and glial fibrillary acidic protein (GFAP) was used to evaluate astrocyte activation 72 hours after the injection of 50µg/Kg of NG291. NG291-treated animals have shown infiltration of Evans Blue to the brain parenchyma and accumulation in the ventricles showing an increase of BBB permeation 24 hours after the injection. The water content of the brain did not increase with NG291 treatment. 72 hours after the treatment the histology using Fluoro-Jade and GFAP did not show significant changes when compared to controls. Normal BBB permeability can be increased using NG291. In future studies, this peptide will be used to facilitate the delivery of pralidoxime into the brain and therefore increase the overall effect of this drug.

Disclosures: S.R. Masso: None. **S. Martinez:** None. **V.A. Eterovic:** None. **P.A. Ferchmin:** None. **A.H. Martins:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.15/NN14

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH NINDS R211NS090282

Title: Impact of western versus omega-3 diets on mfsd2a expression

Authors: K. E. SANDOVAL[1], J. S. WOOTEN[2], M. L. SCHALLER[2], M. P. HARRIS[2], *K. A. WITT[3]
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Abstract: Major facilitator super family domain containing 2a (mfsd2a) transports the omega-3 fatty acid, docosahexaenoic acid (DHA), and other long-chain fatty acids in the form of lysophosphatidylcholine across the blood-brain barrier. While Mfsd2a alterations have been shown to be important in the formation and integrity of the blood brain barrier, it remains unclear how diets with different types and percentages of fatty acids may impact its expression in adult animals. To examine this association, C57BL/6 mice were treated with diets of: 10% lard, 10% fish oil, 41% lard or 41% fish oil for 32 weeks starting at eight weeks of age. Cerebral cortex and subcortical (hippocampus, amygdala, thalamus, caudate) tissues were respectively assessed and evaluated for changes in protein (Western Blot; n=6/group) and mRNA (RT-PCR; n=12/group) expression relative to the 10% lard diet.
Diet significantly impacted the change in weight over the course of the study ($p<0.05$) and glucose tolerance at 31 weeks ($p<0.05$). The type of diet was a significant predictor of cortical mfsd2a protein expression ($p<0.05$). Cortical Mfsd2a protein expression was significantly higher in mice receiving 10% fish oil ($p<0.05$), 41% fish oil ($p<0.05$) or 41% lard ($p<0.05$) when compared to mice receiving a 10% lard based diet. The type of diet was found to be a significant predictor of subcortical mfsd2a protein expression ($p<0.05$). Subcortical Mfsd2a protein expression was significantly higher in mice receiving the 41% fish oil diet ($p<0.05$) or 41% lard diet ($p<0.05$) when compared to mice receiving the 10% lard diet. No significant differences were identified as to mfsd2a mRNA expression. This study shows that fish oil based diets and high-fat lard diets increase protein expression of Mfsd2a compared to 10% lard based diet.

Disclosures: K.E. Sandoval: None. **J.S. Wooten:** None. **M.L. Schaller:** None. **M.P. Harris:** None. **K.A. Witt:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

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Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: University of Wisconsin-Madison School of Pharmacy

UW Institute for Clinical and Translational Research (NIH UL1TR000427 and KL2TR000428)

Wisconsin Alumni Research Foundation

Clinical Neuroengineering Training Program fellowship (NIH NRSA T32 EB011424)

National Science Foundation fellowship (DGE-1256259)

Title: Intrathecal administration of antisense oligonucleotides: CNS distribution and implications for neurodegenerative disease treatment

Authors: *B. WILKEN-RESMAN[1], M. E. PIZZO[1,2], E. BRUNETTE[7], N. KUMAR[1], K. VANG[3], G. GREENE[1], D. B. STANIMIROVIC[7], R. G. THORNE[1,2,4,5,6]
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Abstract: Clinical trials are ongoing for several intrathecally-administered macromolecule therapeutics, including antisense oligonucleotide (ASO) therapies in patients with neurodegenerative diseases such as Huntington's Disease, familial amyotrophic lateral sclerosis (ALS), and spinal muscular atrophy. ASOs are typically ~7 kDa single-stranded DNA oligomers and are particularly attractive therapeutic candidates for diseases caused by known genetic abnormalities because they can specifically manipulate target mRNA to enable or restore normal protein synthesis. ASOs must be administered centrally because of limited-to-nonexistent blood-brain barrier (BBB) penetration. However, despite the common use of the intrathecal route for most ASO studies to date, the CNS distribution of ASOs after intrathecal administration has not been well described. There are thought to be two primary transport mechanisms governing the distribution of macromolecules in the brain: diffusion in the extracellular spaces and convective flow in perivascular spaces surrounding the cerebral vasculature. Here, we investigated the diffusion and CNS distribution of 19-mer phosphorothioate-modified ASOs covalently attached to either DyLight488 or AlexaFluor488 fluorophores. ASO hydrodynamic properties were first characterized by measuring free diffusion in agarose using integrative optical imaging (IOI),

yielding free diffusion coefficients of 1.53 ± 0.05 x 10^{-6} cm^2/s (mean ± sem; *n*=26) and 1.88 ± 0.03 x 10^{-6} cm^2/s (mean ± sem; *n*=29) for DL488-ASO and AF488-ASO, respectively, and hydrodynamic diameters of approximately 4 nm for each. Intrathecal administration of each ASO was performed in rats and the distributions were visualized using *ex vivo* fluorescence imaging and confocal microscopy. ASO distribution to perivascular spaces was markedly less than that of a protein macromolecule of similar hydrodynamic diameter, regardless of the fluorophore used, suggesting ASOs experience additional sources of hindrance aside from their size that limit their distribution in the brain (e.g., electrostatic interactions). Co-infusion with a hyperosmolar solution has been shown to be an effective method to enhance perivascular access from the CSF, a strategy that may also be effective in improving the brain delivery of ASOs to additional regions and deeper areas. Our data provides key guidance for understanding the potential/limitations of central ASO delivery strategies and the resulting distribution to be expected with intrathecal infusion. It may also lead to new methods to enhance the CNS delivery of ASOs for the treatment of a variety of neurodegenerative diseases.

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Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.17/NN16

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Innóvate Perú N-135-PNICP-PIAP-2015

NIH training grant FIC/NIH D43 TW001140

NIH grant 5D43TW006581

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Title: Vascular abnormalities in a rat model for neurocysticercosis

Authors: *R. P. CARMEN[1], D. G. DÁVILA[1], R. GILMAN[2], Y. CAUNA[1], N. CHILE[1], A. D. DELGADO[1], J. D. MORALES[1], G. CASTILLO[1], L. E. BAQUEDANO[1], R. H. CELIZ[1], M. R. VERASTEGUI[1]
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Abstract: Neurocysticercosis (NCC) is the main brain infectious disease affecting people in developing countries and the study of this pathology is scarce. Common lesions reported in NCC patients include the presence of reactive gliosis, inflammatory infiltrates and vascular changes. NCC pathology varies depending on cyst location and viability. Since clinical manifestation of this infection generally occur when the parasite starts degenerating, the progression of NCC is not well understood and animal models have been used to explore NCCpathology. There is a link between vascular changes and blood-brain barrier (BBB) alteration in many neurological disorders. To explore vascular abnormalities presented in NCC we used an animal model for NCC. Holtzman rats (12-15 days old) were injected intracranially with T.solium activated oncospheres (n=18) and saline for controls (n=8). After 3 months of infection 13 rats developed viable cysts. Animals were euthanized and the pathology was studied using immunohistochemistry. We found vascular abnormalities in the tissue surrounding the cyst. Alterations include dilated vessels and fibrotic vessels detected by Masson trichrome staining. These fibrotic vessels showed a reaction to fibrinogen protein. Additionally, different cells presented strong reaction to desmin, alpha-smooth muscle actin, and platelet-derived growth factor receptor beta. Interestingly, dilatated vessels presented low expression of the endothelial brain barrier antigen reflecting BBB compromise. Together this data shows that vascular changes in NCC include an increase in vascular caliber and changes in its structure were endothelial cells, pericytes, and smooth muscle cells could be affected resulting in the possible alteration of the BBB. Whether this vascular changes could contribute to NCC pathology or could be exacerbated in degenerated cyst has to be addressed in future studies.

Disclosures: **R.P. Carmen:** A. Employment/Salary (full or part-time):; Infectious Diseases Laboratory Research-LID, Faculty of Science and Philosophy, Universidad Peruana Cayetano Heredia. 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.; Department of International Health, Bloomberg School of Hygiene and Public Health, Johns Hopkins University. **D.G. Dávila:** None. **R. Gilman:** None. **Y. Cauna:** None. **N. Chile:** None. **A.D. Delgado:** None. **J.D. Morales:** None. **G. Castillo:** None. **L.E. Baquedano:** None. **R.H. Celiz:** None. **M.R. Verastegui:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.18/NN17

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: R21NS090282

Title: Impact of western versus omega-3 based diets on glut-1 expression

Authors: K. A. WITT[1], J. S. WOOTEN[2], M. L. SCHALLER[2], M. P. HARRIS[2], *K. E. SANDOVAL[3]
[1]Pharmaceut. Sci., Southern Illinois Univ. Edwardsville, Edwardsville, IL; [2]Applied Hlth., [3]Pharmaceut. Sci., Southern Illinois Univ., Edwardsville, IL

Abstract: The glucose transporter-1 (glut-1) regulates glucose across the blood-brain barrier, serving as a key regulator of brain energy. This study assesses how diets with different types and percentages of fatty acids may impact glut-1 expression in adult animals. To examine the association between diet, glucose tolerance and expression of glut-1, C57BL/6 mice were treated with either a 10% lard, 10% fish oil, 41% lard or 41% fish oil diet for 32 weeks starting at eight weeks of age. Cerebral cortex and subcortical (hippocampus, amygdala, thalamus, caudate) tissues were respectively assessed and evaluated for changes in protein (Western Blot; n=6/group) and mRNA (RT-PCR; n=12/group) expression relative to the 10% lard diet. Poorer glucose tolerance at 31 weeks was observed in mice receiving the 41% lard based diet compared to mice receiving 41% fish oil ($p<0.05$) or 10% fish oil ($p<0.05$). However, neither glucose tolerance or weight change were predictors of cortical or subcortical glut-1 protein expression. Cortical glut-1 protein expression was higher in mice receiving the 41% fish oil diet ($p<0.05$) and the 41% lard diet ($p<0.05$), compared to 10% lard based diet. Subcortical glut-1 protein expression was significantly higher in mice receiving the 10% fish oil diet ($p<0.05$), 41% fish oil diet ($p<0.05$) and 41% lard diet ($p<0.05$), compared to 10% lard based diet. No significant differences were identified as to glut-1 mRNA expression. This study shows that 41% lard and 41% fish oil diets in the cortical and subcortical, and 10% fish oil in the subcortical, increase glut-1 protein expression compared to 10% lard diet.

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Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.19/NN18

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: TTUHSC Institutional Funds

Title: Modelling the diseased blood-brain barrier using patient-derived stem cells: Making a case about Batten’s disease and Familial form of Alzheimer’s disease

Authors: *R. PATEL, A. ALAHMAD
Pharmaceut. Sci., Texastech Univ. Hlth. Sci. Ctr., Amarillo, TX

Abstract: ***Background:*** The blood-brain barrier (BBB) constitutes physical and chemical barrier formed by specialized brain endothelial cells (BMECs) surrounded by astrocytes, pericytes and neurons. Such barrier plays an essential role in the maintenance of the brain homeostasis. More recently, several studies highlighted the contribution of a dysfunctional BBB in several neurological disorders, particularly in neurodegenerative disorders such as Alzheimer's disease or Huntington's disease. Yet, the impact of genetic factors involved in certain neurodegenerative disorders on the BBB function remains unclear. In this study, we demonstrated the impact of such genetic factors on the BBB function using an isogenic model of the BBB based on induced pluripotent stem cells (iPSCs) ***Methods:*** We used iPSC derived from patients suffering from Batten's disease (BD, CLN3 mutation) and from an early onset familial form of Alzheimer's disease (eFAD, PSEN1 mutation). We differentiated all iPSCs to astrocytes, BMECs and neurons using differentiation protocols established in our lab. We characterized each differentiated cell types using cell-specific markers and for the presence of biological features associated with such disorders (e.g. lipofuscin accumulation for BD patients). In addition, we investigated changes in barrier properties (using TEER and fluorescein permeability) and transporters activity (e.g. Amyloid β (Aβ) peptide clearance across BMECs) ***Results:*** Preliminary data obtained from BD patients suggest the presence of a dysfunctional barrier as we noted lower barrier tightness in CLN3-derived BMECs compared to IMR90-derived BMECs (asymptomatic control) monolayers. CLN3-derived BMECs showed the presence of lipofuscin inclusion bodies. In the other hand, iPSC-derived BMECs showed the presence of an active diffusion of Aβ 1-40 across IMR90-derived BMECs, such diffusion occurred through a transcellular manner. ***Discussion:*** In this study, we demonstrated the ability to differentiate a BBB model from patients suffering from neurodegenerative diseases. Our preliminary data suggest that such mutations also impact non-neuronal cells, in particular cell types present at the BBB (BMECs and astrocytes). Our future direction is focused on using such model to demonstrate the impact of such mutations on astrocytes function by providing side-by-side comparisons in barrier induction in astrocytes/BMECs co-cultures in both BD and eFAD cells, as well as understanding the impact of PSEN1 mutation on Aβ peptides clearance.

Disclosures: R. Patel: None. **A. Alahmad:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.20/NN19

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: TTUHSC Institutional Funds

Laura W. Bush Institute Woman Health Seed Grant

BD Biosciences Stem Cell Award

Title: Modeling ischemic stroke injury at the human blood-brain barrier *In vitro* using patient derived stem cells

Authors: *A. ALAHMAD, S. PAGE
Pharm Sci., Texas Tech. Univ. Hlth. Sci. Ctr., Amarillo, TX

Abstract: *Background:* Stroke constitutes the fifth cause of death and a leading cause of disability in the United States. Most of stroke events are categorized as “ischemic stroke, resulting in an hypoperfusion and hypoxic/ischemic onset. The blood-brain barrier (BBB, a component of the neurovascular unit formed by specialized brain microvascular endothelial cells (BMECs) surrounded by astrocytes, neurons and pericytes) constitutes the first line of cells sensing such stressor. Its disruption constitutes a crucial event in the pathophysiology of stroke injury, yet the mechanism leading to such disruption at the human BBB and the presence of a sexual dimorphism in such disruption remains unclear. In this study, we investigated the cellular response of the human BBB following ischemia/reoxygenation *in vitro*. *Methods:* We used patient-derived induced pluripotent stem cells (iPSCs) derived from males and females asymptomatic control patients. We differentiated such cells into BMECs, astrocytes and neurons following established differentiation protocols. Cells were exposed to oxygen glucose deprivation stress (OGD; 1% O2 and glucose-free medium) for 6 or 24 hours, followed by reoxygenation (Reox). Hypoxia induced factor-1alpha (HIF-1alpha) and VEGF protein levels were assessed by ELISA, cell metabolic activity was assessed by MTT assay. Barrier function was assessed using TEER, fluorescein permeability and immunofluorescence. 10µM CAY105586 or YC1 were used as HIF-1 inhibitors. *Results:* All cells showed a detrimental response to prolonged (24 hours) OGD stress by loss in barrier integrity, decreased cell metabolic activity, loss of neurites (neurons) and increased VEGF secretion. Following OGD/Reox stress, we noted differences in HIF-1alpha protein levels between male and female iPSC lines. Furthermore, such dimorphism was reflected on the barrier recovery during Reox. We noted differences in VEGF secretion between iPSC lines and differences in neurite outgrowth in iPSC-derived neurons. Both CAY or YC1 failed to block HIF1-alpha protein stabilization and showed only minimal effect on the BBB. *Discussion:* Our data suggest a possible sexual dimorphism between male and female cells following response to OGD/reoxygenation stress. OGD-induced barrier disruption appears driven through a HIF-1/VEGF axis, such axis appears to show some differences between sex and individuals. We are currently investigating such differences in terms of changes in cell respiratory metabolism and response to HIF-1 inhibitors.

Disclosures: **A. Alahmad:** A. Employment/Salary (full or part-time):; Texas Tech University Health Sciences Center. **S. Page:** None.

Poster

696. The Blood Brain Barrier in Health and Disease

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 696.21/NN20

Topic: B.10. Network Interactions

Support: FDA/NCTR P00710

FDA/NCTR P00706

Title: Pericytes in the neurovascular unit of a sexually dimorphic nucleus in rats

Authors: *Z. HE, S. A. FERGUSON, M. PAULE
Div. of Neurotoxicology, Natl. Ctr. For Toxicology Res., Jefferson, AR

Abstract: A working module of a neurovascular unit (NVU) in the sexually dimorphic nucleus of the preoptic area (SDN-POA) was proposed (SFN 2016). However, one of the key components, pericytes existing along capillaries and veinules, has not been thoroughly investigated. In this report, male and female weanling rats (n=4-5/sex) were used to define these cells within the SDN-POA. **Methods.** Calbindin D28K (CB28)-immunoreactivity was used to delineate the SDN-POA in which pericytes were tagged with CD13- or alpha-smooth muscle actin (αSMA)-immunoreactivities (irs), two pericyte biomarkers, using two adjacent brain sections (90 micron intervals). Densities of CD13- and αSMA-irs along with SDN-POA volume were compared between males and females after averaging bilateral SDN-POA structures. **Results.** Male SDN-POA was $5.0\pm0.3x10^{-3}$ mm^3 in volume, which was significantly larger than the female ($1.7\pm0.3x10^{-3}$ mm^3, $p<0.05$). Within the SDN-POA, the CD13-irs were characterized as dots, densely packed and net-like in distribution, while the aSMA-irs, excluding pipe-like or circular structures, appeared as short rod-like structures that were relatively sparsely distributed. The short rod-like aSMA-irs counts were $353\pm57/mm^2$ in males and $124\pm46/mm^2$ in females ($p<0.05$). On the other hand, densities of the dot-like CD13-irs were $4009\pm301/mm^2$ in males and $4018\pm414/ mm^2$ in females (not significant at $p>0.05$). Accordingly, we propose that a subset of capillary pericytes is aSMA-positive and likely functions (dependent upon their aSMA-associated structure and physiology) to control the local blood-brain barrier. Since the majority of pericytes within the SDN-POA were aSMA-negative, they likely function differently. Future studies using larger group sizes are warranted to verify whether pericytes that selectively express aSMA do so in a sex-dependent fashion in the SDN-POA.

Disclosures: Z. He: None. **S.A. Ferguson:** None. **M. Paule:** None.

Poster

697. Motivation: Subcortical Neurocircuitry

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 697.01/NN21

Topic: G.02. Motivation

Support: NIH Grant NS23805

Title: Zona incerta as a substrate for orchestration of adaptive responding - variation on a theme by John Mitrofanis (Neuroscience 130:1-15, 2005)

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Abstract: Motivation arises due to innate (e.g., hoard, nest, mate) and homeostatic (e.g., eat, drink, relocate) imperatives, and cues signaling threat or reward (usually related to such imperatives). The medial forebrain bundle (mfb) is the common pathway for outputs subserving motivation. Signals descending in the mfb directly modulate adaptive responses like, e.g., locomotion and acoustic startle, but, due to not reaching to spinal motor networks, having relatively weak projections to brainstem effector sites and targeting (via thalamus) mainly cortical association rather than motor/premotor areas, mfb cannot orchestrate complex adaptive behavior. Zona incerta (ZI), in contrast, has strong connections with brainstem and spinal motor sites and is strongly and reciprocally connected with sensorimotor cortex, rendering it suitable to enlist movements, which stimulating ZI actually does. Inactivating ZI blocks movement caused by stimulating the mfb. We have undertaken to provide a better characterization of input to ZI from motivation-related structures (i.e., that project via the mfb). Using new and archived cases and some reports published by others, anterogradely transported Phaseolus vulgaris-leucoagglutinin (PHA-L) and, in a few cases, biotinylated dextran amine (BDA) were mapped in the subthalamic region of rats following injections into motivation-related brain structures. Injection sites were selected from maps of retrograde labeling produced by injection of cholera toxin β subunit into the rostral (r) subdivision of the ZI (SfN Abstr 708.02, 2015). ZIr was distinguished from the underlying dorsolateral (dl) lateral hypothalamus (LH) with antibodies against tyrosine hydroxylase. LHdl received dense projections from many evaluated structures, including the prefrontal cortex, lateral septum, ventral pallidum, bed nucleus of stria terminalis, sublenticular extended amygdala and central amygdala, of which all sent additional sparse projections into rZI. However, tracer injections into the lateral preoptic area and LH, particularly LHdl, produced moderate ZIr labeling and yet more robust ZIr labeling was generated by tracer injections along the descent of the mfb, particularly in the retrorubral area, lateral, ventrolateral and precommissural periaqueductal gray and the pedunculopontine, laterodorsal tegmental and

parabrachial nuclei. Projections from widespread motivation-related structures thus may converge at several nodes, which, collectively, provide a robust input to the ZIr. Insofar as all parts of the ZI are robustly interconnected, activity throughout the entire ZI may be modulated by motivation-related signals.

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Poster

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Title: Elucidating the role of the supramammillary nucleus in motivational processes

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Abstract: Motivational capacity to interact with the environment is fundamental for everyday healthy living. Motivated behaviors ultimately manifest through reward and aversion processes, where animals must approach positive 'rewarding' stimuli and avoid negative 'aversive' stimuli to survive. The supramammillary nucleus (SuM), is a small posterior hypothalamic nucleus that provides dense projections throughout the cerebrum. Past research on SuM has focused on its role in arousal, learning, and memory. Our lab previously found that pharmacological stimulation of SuM neurons can reinforce behavior, leading us to further investigate the role the SuM and its related circuitry plays in reward and motivation. We first confirmed stimulation of SuM neurons is rewarding using a self-stimulation procedure with optogenetics involving *channelrhodopsin-2* (ChR2) in wild-type (C57/BL6) mice. Mice with ChR2 and optic fibers in SuM quickly learned to respond on a lever reinforced by photostimulation and switch responding when lever assignments are reversed. Mice do not reliably self-stimulate when optic fibers are placed in areas adjacent to SuM, ie. in the mammillary bodies or ventral tegmental area. Next, using a Cre-dependent ChR2 and vGlut2-Cre, vGat-Cre or Th-Cre mice, we show this rewarding effect of SuM neuron stimulation is likely mediated by glutamatergic neurons, but not dopaminergic or GABAergic neurons. Then, using optogenetic terminal-stimulation we dissect which glutamatergic projections from the SuM mediate self-stimulation behavior. Mice learned to respond for the stimulation of SuM glutamatergic neurons terminating in the septal area, but not terminals in the paraventricular thalamic nucleus (PVT), ventral subiculum, or diagonal band

of Broca. In addition, mice show real-time place preference for activation of the SuM to septum circuit, and real-time place aversion for activation of the SuM to PVT circuit, indicating bivalent affective processes driven by SuM circuitry. To investigate the role of SuM neurons in food taking and seeking behaviors, we conducted single-unit in-vivo electrophysiology experiments in mice seeking sucrose, a natural reward. Most SuM neurons change their firing rates as a function of sucrose seeking, taking, or both. Our results implicate the SuM and its downstream targets in motivational processes. As this circuitry is somewhat non-canonical in terms of classical reward circuits, we feel it warrants future research into its role in psychiatric disorders such as depression and addiction.

Disclosures: **A. Kesner:** None. **S. Ikemoto:** None.

Poster

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HFSP RGY0076/2012 (TK)

GIF I-1326-421.13/2015 (TK)

Title: Coordinated gamma oscillations in the lateral septum and the lateral hypothalamus drive food seeking

Authors: *M. CARUS-CADAVIECO[1], M. GORBATI[1], L. YE[2], F. BENDER[1], S. VAN DER VELDT[1], N. DENISOVA[1], F. RAMM[1], K. DEISSEROTH[2], A. PONOMARENKO[1], T. KOROTKOVA[1]
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Abstract: Cortical cognitive processing involves gamma oscillations, which support memory, attention and behavioral flexibility. These functions crucially contribute to feeding behavior, however, the underlying neural mechanisms are unknown. Lateral hypothalamus (LH) is crucial for regulation of feeding, yet little is known about the regulation of LH by top-down inputs from cognitive control regions. Top-down forebrain innervation of LH is provided, to a large extent, by inhibitory inputs from the lateral septum (LS), a key region for governing innate behaviors according to environmental context; LS is connected, in turn, with cortical networks. Here we

combined optogenetics and electrophysiological high-density recordings in mice during spontaneous behavior in a free-access feeding paradigm. We found that LS and LH displayed prominent gamma oscillations (30-90 Hz) which entrained neuronal activity within and across the two regions (Carus-Cadavieco et al., Nature, 2017). When mice engaged in approach to the food zone, the power of gamma oscillations in LS and LH matched the time required to reach the food zone, but not the drinking zone. Optogenetic gamma-frequency stimulation of somatostatin-positive (LS-SST) projections to LH facilitated food-seeking, i.e. shortened latency to reach the food zone but not the drinking zone or a control zone. It also increased probability of entering the food zone prior to food-free zones, located in other corners of the enclosure. Optogenetic inhibition of the LS-SST-LH pathway during food approach reduced food seeking. LS inhibitory input enabled separate signaling by LH neurons according to their feeding-related activity, making them fire at distinct phases of the gamma oscillation. In contrast to increased food intake during optogenetic stimulation of LH Vgat cells, food intake during gamma-rhythmic LS-LH stimulation was not changed. Accordingly, we identified that LS-LH gamma-rhythmic input regulate activity of function-selective subgroups of LH cells in a different way than activation of LH Vgat neurons. Upstream, we identified medial prefrontal cortex projections providing gamma-rhythmic inputs to LS, leading to improved performance in a food-rewarded learning task. Overall, our work identifies a novel top-down pathway, which utilizes gamma synchronization to guide activity of subcortical networks and to regulate feeding behavior by dynamic reorganization of functional cell groups in hypothalamus. This study is supported by the DFG (Exc 257 NeuroCure, TK and AP, Priority Program 1665, 1799/1-1(2), AP), The Human Frontier Science Program (HFSP; RGY0076/2012, TK, DB), and GIF (I-1326-421.13/2015, TK).

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Poster

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DFG, SPP 1665, 1799/1-1(2) (AP)

HFSP, RGY0076/2012 (TK)

GIF, I-1326-421.13/2015 (TK)

Title: Gamma-rhythmic input from the medial prefrontal cortex to the lateral septum regulates performance in a food-rewarded learning task

Authors: M. GORBATI[1], M. CARUS-CADAVIECO[1], L. YE[2], F. BENDER[1], Y. HU[1], C. BÖRGERS[3], N. DENISOVA[1], S. LEE[2], C. RAMAKRISHNAN[2], E. VOLITAKI[1], K. WEINECK[1], K. DEISSEROTH[2], *T. KOROTKOVA[4,1], A. PONOMARENKO[1]
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Abstract: Goal - directed behaviors are thought to involve top-down representations of cognitive and emotional information to subcortical regions. Projections from the lateral septum (LS) to midbrain and lateral hypothalamus support drug- and food-seeking (Luo et al., Science, 2011, Carus-Cadavieco et al., Nature, 2017), with the latter utilizing gamma oscillations (30-90 Hz). Gamma oscillations enable synchronization and communication between neuronal populations and play an important role in memory, attention and sensory responses. To study circuitry providing gamma-rhythmic signaling to LS we combined optogenetics, local field potential (LFP) and multisite unitary electrophysiological recordings in freely behaving mice, CLARITY and computational modeling. A biophysical network model of LS demonstrated locally generated gamma rhythm which was further stabilized by external, weakly oscillating at gamma frequency, input. LS and its prominent excitatory input, hippocampus, were weakly coherent at gamma frequencies. Conversely, we found co-occurrence of gamma LFP epochs in LS and mPFC and increased gamma coherence of current flow density in the LS with LFP in mPFC. CLARITY revealed prominent fibers of CaMKIIa-expressing mPFC neurons terminating in the LS. The firing of LS cells during gamma oscillations was preceded by an increased discharge of mPFC neurons, the precision of co-firing between LS and mPFC predicted phase lags between concurrent LFP gamma cycles in these regions. Recordings from mPFC and LS as the animals performed a food-rewarded learning task in the T-maze revealed that correct choices were associated with an increased count of fast (60-90 Hz) and slow (30-60 Hz) gamma oscillation episodes in mPFC and LS selectively during the choice phase of the task but not in the start arm of the T-maze. Optogenetic stimulation of mPFC-LS projections at gamma frequency led to an increase of the number of correct trials in the T-maze and improved temporal stability of the performance, increasing fraction of repeated correct trials compared to repeated incorrect trials. The inhibition of mPFC-LS projections led to an opposite effect, decreasing the performance in the T-maze. These results suggest that signaling from the mPFC to the LS is coordinated by gamma oscillations, which regulate goal-directed behavior in a food-rewarded task. This study is supported by the DFG (Exc 257 NeuroCure, TK and AP, Priority Program 1665, 1799/1-1(2), AP), The Human Frontier Science Program (HFSP; RGY0076/2012, TK), and GIF (I-1326-421.13/2015, TK).

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Poster

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The Human Frontier Science Program (HFSP; RGY0076/2012, TK, DB)

Title: Role of theta rhythmic signaling from hippocampus to lateral septum during exploratory behaviour

Authors: *F. BENDER[1], M. GORBATI[2], M. CARUS-CADAVIECO[2], N. DENISOVA[2], X. GAO[2], C. HOLMAN[2], T. KOROTKOVA[2,3], A. PONOMARENKO[2]
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Abstract: During locomotion, frequency of hippocampal theta oscillations (5-12 Hz) changes with running speed. However, the relationship between theta synchronization and motor output is complex. Hippocampal theta rhythm is modulated via the medial septum, which is considered the fundamental theta pacemaker. It receives ascending inputs from several brainstem areas and forwards sensory signals to the hippocampus. Medial septal parvalbumin-positive GABAergic cells synapse onto interneurons in the hippocampus CA1 and can thus rhythmically release pyramidal cells from inhibition. The entrainment of various neuronal types during theta oscillations is highly coordinated within and across hippocampal lamina and coherent across hemispheres. The lateral septum is the main subcortical output region of the hippocampus, receiving massive excitatory inputs from hippocampal pyramidal cells. Yet, little is known about the interactions between these regions. The lateral septum is a key element in circuits governing expression of innate behaviours according to environmental context, possibly by regulating communication from cortical to subcortical structures. A major efferent of the lateral septum, the lateral hypothalamus, comprises the diencephalic locomotion region, that provides downstream motor circuits with direct commands for movement. Combining optogenetic control of hippocampal theta oscillations with electrophysiological recordings in mice, we found that hippocampal theta oscillations regulate locomotion. Higher theta regularity caused more stable and slower running speeds during exploration and was accompanied by more regular theta-rhythmic spiking output of hippocampal pyramidal cells. Theta oscillations were coordinated between the hippocampus and the lateral septum. Both chemo- (DREADDs) and optogenetic

inhibition of this pathway revealed its necessity for the hippocampal regulation of running speed. Moreover, theta-rhythmic stimulation of lateral septum projections to the lateral hypothalamus replicated the reduction of running speed. These results suggest that changes in hippocampal theta synchronization are translated into rapid adjustment of running speed via the lateral septum.

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MH101506

Title: Diffusion-imaging derived cell density in the nucleus accumbens core predicts delay discounting in humans

Authors: *J. J. CASTRELLON[1], K. H. KARLSGODT[2,3]
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Abstract: Structural brain imaging studies of impulsivity in humans have largely implicated the nucleus accumbens (NAc). However, most such studies lack the spatial resolution or tissue modelling to distinguish the complex cellular composition of the NAc. The core (NAcc) and denser shell (NAcs) subregions present dissociable relationships with delay discounting (DD)—a feature of impulsivity—in rodents that received either NAcc or NAcs lesions. Specifically, while the core is critical to DD, the shell serves other functions. Given the dissociable roles in rodents, it may be speculated that similar specific associations might drive impulsivity in humans. We therefore used high-resolution multi-shell diffusion-weighted imaging (DWI), spatial modelling, and data-driven source estimation of human brains *in vivo* to derive spatial components of NAc cell density. Further, we tested associations between DD and NAc cell density in identified subregions. High-quality minimally-preprocessed DWI data for 80 healthy unrelated adult participants were examined from the Human Connectome Project dataset. Participants also completed a DD task for hypothetical monetary rewards. Voxelwise maps of neurite orientation and dispersion density (NODDI) were calculated for each participant. From these NODDI maps, a histologically-validated tissue model was fit to derive compartment estimates representing cellular density. Cell density maps were submitted to an independent component analysis (ICA) to derive subregional spatial maps within *a priori* masks of the left and right NAc. Component

maps were compared with known histological features of the NAc. Linear regressions were run on participant loading scores for components of interest with age and sex as covariates to predict DD. An intensity gradient that delineates the NAcc and NAcs emerged from cell density maps. Consistent with past findings, better DD was positively correlated with a cell density component in the right NAcc but not the NAcs. The findings present a promising role for DWI in translational models of cellular microstructure. The positive correlation with DD seen specifically in the NAcc highlights the importance of considering the heterogeneous composition of the NAc when investigating its role in governing impulsive choices.

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Poster

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Title: Effects of inhibiting the lateral preoptic area and ventral pallidum on psychostimulant induced and basal locomotion

Authors: *R. A. REICHARD, S. SUBRAMANIAN, K. P. PARSLEY, D. S. ZAHM
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Abstract: The lateral preoptic area (LPO) and ventral pallidum (VP) are output structures serving mainly the septal-preoptic and ventral striatopallidal sectors of the basal forebrain. We showed earlier that locomotor activation is much more robustly increased by disinhibition of the LPO than VP. Further, disinhibition of the VP, but not LPO, is accompanied by dyskinesia and compulsive ingestion. We here extend the comparison to the locomotor effects of inhibiting LPO and VP. Guide cannulae targeting the VP or LPO were implanted into groups of Sprague Dawley rats. After a week of recovery, the rats received subcutaneous injections of D-amphetamine (1.0mg/kg) ten minutes prior to testing in activity monitors. Locomotion was recorded for 12 minutes before the GABA(A) receptor agonist, muscimol (74ng/0.25µl/min), or an equivalent volume of saline was infused bilaterally into the VP or unilaterally into the LPO. They were then tested for thirty minutes more. High locomotor counts (4542 ± 487[mean ± SEM]) were maintained following saline infusions. LPO muscimol infusions significantly reduced locomotor counts [2294 ± 526; $t(22)=3.37$, $p=0.006$ compared to pooled saline infusions], whereas VP muscimol infusions almost completely suppressed locomotion [112 ± 34; $t(22)=6.65$, $p<0.001$ compared to pooled saline; $t(22)=2.87$, $p=0.009$ compared to LPO muscimol]. Additional experiments produced similar effects following bilateral LPO and unilateral VP infusions of

muscimol. To determine the effects on basal locomotion, separate experiments were conducted. During the second hour of the dark cycle, when basal activity is maximal, bilateral infusions of muscimol into either structure nearly abolished locomotion [VP: 243 ± 51; LPO: 260 ± 59; pooled saline: 243 ± 51; pooled saline vs VP: $t(11)=4.52$, $p=0.003$; pooled saline vs LPO: $t(11)=4.05$, $p=0.004$]. Thus, like disinhibition, inhibiting VP and LPO distinguishes these two important forebrain structures, which the data indicate have contrasting roles in the inhibition of locomotion elicited by D-amphetamine but, not basal locomotion. Whether the differences reflect distinct connectivity with dopamine neurons vs. downstream behavioral effectors requires further investigation. However, we can surmise that the LPO and VP activation and inhibition data, together with the failure of VP activation to alter ventral tegmental area dopamine neuron activity (Floresco et al., 2003, Nat Neurosci 6:968-73), support a model in which activation of the LPO, but not VP, facilitates dopamine release in the accumbens (Acb) and the locomotor activating property of Acb dopamine release is conveyed to behavioral effectors through the VP but not LPO.

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Fronteras de la Ciencia 63.

Productos Medix

Title: Animals can use optogenetic-induced brain activations of the prefrontal cortex or the nucleus accumbens shell, as a predictive cue to avoid punishment and to obtain rewards

Authors: *J. LUIS[1], B. DURAN-SOSA[2], G. B. FLORAN[2], R. GUTIERREZ[2]
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Abstract: Several brain manipulations (either electrical or optogenetic) have been used to perturb the brain activity in order to evaluate their sufficiency -or necessity- of a particular behavior. Nevertheless, these brain perturbations can generate interoceptive cues that can be used to guide behavior. The majority of studies have focus in the somatosensory cortex (S1), however we reason that any brain region will be able to generate such interoceptive states. We hypothesize that pairing an arbitrary optogenetic stimulation, regardless of the brain region, with

a relevant behavioral event, will induced plasticity on brain circuits normally associated to that event, such as now the optogenetic activation will be able to drive behavior. To test this idea, we used the Thy1-ChR2 mice to photoactivate either cortical pyramidal neurons from layer V (in prefrontal cortex, PFC) or its fibers inputs to the nucleus accumbens shell (NAcSh). Thy1-ChR2 mice were trained in a two sipper sucrose alternating task, where -in order to receive two drops of sucrose- they had to alternate between two opposite left and right sippers (Phase 1). Additional licks in the rewarded sipper will no longer release more sucrose, until mice licked the opposite sipper. In half of trials, when the subject heads halfway toward the opposite port, a 1 s train of photostimulation (20Hz) + a tone were delivered, mice uses these cues to change its direction and return to the previously rewarded port to be rewarded again with sucrose. If they continued and lick the opposite sipper, mice were punish (with 2 airpuffs). After learning, the tone was removed and phase 2 begins: the subjects had to predict punishment only using photostimulation. We found that transgenic mice can avoid punishment, by only using the photostimulation cue (tone off). Photoactivations of PFC and NAcSh induced the same performance, and transgenic mice learned Phase 1 -30 sessions- faster than wild-type mice, suggesting that the photostimulation was better cue than the tone itself. Thus, optogenetic stimulation can be a predictive signal of an outcome, regardless of its original function. Finally, we tested if subjects can learn different rules by discriminating between 2 photostimulation frequencies (e.g., 20 Hz indicates continue and 1 Hz return). We found that subjects can discriminate between the 2 frequencies. In summary, we demonstrate that arbitrary optogenetic evoked brain activations can be interoceptive cues, and animals can use specific frequencies to generate different behaviors. This work paves the way to investigate how artificial network's activations are associated via pavlovian learning to avoid punishment or to obtain rewards.

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Topic: G.02. Motivation

Support: Problemas Nacionales 464

Fronteras de la Ciencia 63

Productos Medix

Title: Optogenetic stimulation of lateral hypothalamus GABAergic neurons in a closed-loop open-field task elicits place preference and increases consumption of the nearest most salient stimuli

Authors: *A. I. HERNANDEZ-COSS[1], J. LUIS-ISLAS[2], A. GARCÍA-GUTIÉRREZ[2,3], L. PURÓN-SIERRA[2], D. ELÍAS-VIÑAS[1], R. GUTIERREZ[2]
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Abstract: Although many studies have linked the Lateral Hypothalamus (LH) with feeding and reward, the specific mechanisms through which the LH controls reward, appetitive and consummatory behaviors is not yet clear. When presented with different food stimuli, electrical stimulation of the LH increases consumption of a preferred stimulus, this led to the idea that electrical stimulation in the LH induces a "stimulus bound" and that it depends on the subject's latent preference. However, it is not known how LH GABAergic neurons participate when several food stimuli are simultaneously presented and the mice self-stimulate these neurons. We addressed this by using Vgat-ChR2 mice to photoactivate LH GABAergic neurons and by designing a novel closed-loop open-field task, where several food stimuli are present simultaneously in a circular arena. Sated mice were placed in the center of the arena, equidistant to three different stimuli plates containing cork, food chow, chocolate pellets and a sipper with 10% sucrose solution. For 30 minutes an online computer vision program tracks the position of the subject and when it enters an area at the center of the arena it triggers a train of blue light pulses (473 nm, 50 Hz, 15 mW, 2 s on 4 s off). We found that all mice robustly self-stimulate by crossing and/or staying at the center spot of the arena, and although the consumption of food increased it varies between subjects, with some animals preferring chow, others sucrose, in a non-consistent pattern. When the area that triggers the optogenetic stimulation was relocated from the center to a different place of the arena (e.g., to the area around the pellet) we observed that the subjects remained for a longer time on the new stimulation area, even when paired to a food that was previously uninteresting to them, as was the case with the chocolate pellet (the most novel stimuli) until it was paired with the optogenetic stimulation. We also observed an increase of the spill and consumption of the food stimuli nearest to the optogenetic stimulation sites. In summary, our results indicate that our closed-loop optogenetic activation of LH GABAergic neurons in LH induces a robust place preference and increases food intake of the nearest food item, regardless of the subject's previous preference. The closed-loop open-field stimulation task is robust enough to override stimulus-bound behaviors previously observed in open-loop stimulation tasks. Thus, our data indicates that activation of LH GABAergic neurons is rewarding and it can dynamically re-shape the saliency of the nearest food stimuli.

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Poster

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Topic: G.02. Motivation

Support: Productos Medix

Problemas Nacionales 464

Fronteras de la Ciencia 63

Title: Activation of the lateral hypothalamus GABAergic neurons that promote consummatory behavior depends on the proximity and palatability of the stimulus

Authors: *D. A. GARCÍA[1,2], J. LUIS-ISLAS[2], A.-I. HERNANDEZ-COSS[2], L. PURON-SIERRA[2], R. GUTIERREZ[2]
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Abstract: Recently, it was found that optogenetic stimulation of LH GABAergic neurons produce appetitive and consummatory behaviors, regardless of nutritional value and activation of these neurons induced approach behavior to the closest salient stimulus. We reasoned that these behaviors can be influenced by the palatability (or attractiveness) of the stimulus. To test this idea, satiated Vgat-ChR2 transgenic mice, which express ChR2 in LH GABAergic neurons, were trained in a novel open loop task that consisted in an operant box with three ports. The left port contains 3% sucrose, the central port -water-, and the right lateral port -18% sucrose-. Taste solutions were available all times. We found that transgenic mice increased consumption of 18% sucrose in 5 min laser on blocks compared to 5 min off blocks. These results can be explained because the mice spent more time near the most palatable stimulus (18% sucrose) and thus during optogenetic stimulation (2s on 4s off) they consume more 18% sucrose. We then asked whether activation of LH GABAergic neurons promote the consumption of the more palatable stimulus or the nearest although less palatable stimuli. To test this idea we designed a closed loop task, in the same behavioral box described above, but this time the laser was activated when the mice made a head entry in the central port (where water is available). We observed two different behaviors, one group of transgenic mice (n=6) increased their consumption of water (in the central port) over sucrose (lateral port), and another group (n=4) self-stimulate by doing a head entry in the central port, but they do not lick for water instead they move to consumed 18% sucrose, these inter-subjects variability shows that activation of LH GABAergic neurons may modulate two components: proximity and palatability of stimulus. Finally, we replaced water of the central port to either putting: 1) a dry sipper, transgenic mice increased the number of head entries in central port and kept licking the dry sipper; 2) when quinine 3) or airpuffs were given in the central sipper, mice decreased the number of licks, but they maintain a high number of head entries to self-stimulate. 4) However, when we changed the rule to turn on the laser from head entry to lick once the central sipper (i.e., the airpuffs now were inescapable), we found that now mice totally stopped self-stimulation, thus an aversive stimuli is stronger than LH GABAergic neurons activation. Finally; we put 18% sucrose in the central sipper and transgenic mice greatly overconsume sucrose. We concluded that activation of LH GABAergic neurons drives consummatory behavior by an interaction between the proximity and the hedonic value of the stimulus.

Disclosures: **D.A. García:** None. **J. Luis-Islas:** None. **A. Hernandez-Coss:** None. **L. Puron-Sierra:** None. **R. Gutierrez:** None.

Poster

697. Motivation: Subcortical Neurocircuitry

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 697.11/NN31

Topic: G.02. Motivation

Support: MHR01045573

Title: The pallido-subthalamic projection and indirect cortical integration in the subthalamic nucleus

Authors: *C. A. BISHOP, S. R. HEILBRONNER, S. N. HABER
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Abstract: The cortico-basal ganglia network conveys information through direct, indirect, and hyperdirect pathways consisting of open, integrative loops from functionally distinct areas of the cortex. Through such connections, this network is involved in a wide range of psychiatric and neurological disorders, including obsessive-compulsive disorder, addiction, and Parkinson's disease. The subthalamic nucleus (STN) is part of both the indirect and hyperdirect cortico-basal ganglia pathways. The organization of the hyperdirect frontal cortico-STN projection was recently identified as generally topographic, though with convergence along the functional boundaries (Haynes and Haber 2013). The indirect circuity of the BG, on the other hand, has yet been thoroughly charted to the STN. Through this pathway, cortical projections are routed through the striatum and external segment of the pallidum (GPe) and ventral pallidum (VP) before the STN. In this study, our goals were to 1) identify specific pallidal projections to the STN, 2) identify cortical representation within the STN through the indirect cortico-basal ganglia pathway, and 3) compare the indirect and hyperdirect projections within the STN. We used nine cases in which anterograde/bidirectional neural tract tracers were injected into the GPe and VP of macaques. Our database of frontal cortical and striatal injections allowed us to determine the indirect cortical representation in the STN. Results demonstrate a clear pallidal topography within the STN: VP and rostral GPe project medioventrally in the rostral STN, caudal-lateral portions of the GPe project laterally and dorsally within the STN, and caudal-ventral portions of the GPe project centrally within the STN. There is also convergence within this topography such that non-overlapping pallidal injections produce overlapping terminal fields in the STN. Moreover, largely due to such extensive cortical integration within the striatum, cortical divisions of the STN are not as clear through the indirect pathway as compared to the hyperdirect pathway. These results demonstrate the convergent nature of the cortico-basal ganglia circuit. Additionally, they help to identify the distinct functions of the hyperdirect versus indirect

pathways and provide maps of STN afferents that can be used in deep brain stimulation treatment of neurological and psychiatric disorders.

Disclosures: C.A. Bishop: None. **S.R. Heilbronner:** None. **S.N. Haber:** None.

Poster

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Topic: G.02. Motivation

Title: Function dissection of neural circuitry in paraventricular hypothalamus

Authors: *S. XU, H. YANG, F. HENRY, S. M. STERNSON
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Abstract: The paraventricular hypothalamus (PVH) has a major role in controlling behavioral states associated with animal survival functions. It plays important roles in feeding, osmoregulation, stress, grooming, social approach, sexual behavior and regulation of the autonomic nervous system. However, little is known about the integration of functional dynamics of neuronal ensembles in PVH because of the technique challenges caused by its deep-brain location and the intermingled distribution of molecularly defined cell types. To overcome these challenges, here, we report a functional imaging platform that can simultaneously investigate neuronal ensemble dynamics of multiple molecularly defined cell types in a deep-brain structure. GCaMP was pan-neuronally expressed in the PVH. PVH neuron calcium activity was recorded through a GRIN lens by two photon volumetric imaging in awake behaving animals under multiple behavioral states. After in vivo imaging, the brain was sectioned and cell type molecular identity was determined by multiplexed fluorescence in situ hybridization. This platform links traditional system neuroscience ensemble activity measurements with detailed molecular identity of individual neurons in the ensemble, thus it bridges the gap from gene expression to neural dynamics and behavior. Moreover, because this platform does not require genome modification, it's applicable to a large variety of organisms.

Disclosures: S. Xu: None. **H. Yang:** None. **F. Henry:** None. **S.M. Sternson:** None.

Poster

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Topic: G.02. Motivation

Support: NIDA Grant R21DA034929

NIGMS Grant 5T32GM008151-30

Title: A peri-VTA prepronociceptin neuronal system that gates motivation

Authors: *A. M. GOMEZ[1], K. E. PARKER[1], C. E. PEDERSEN[1], S. M. SPANGLER[1], M. C. WALICKI[1], S. FENG[1], R. AL-HASANI[1], G. D. STUBER[4,5], T. L. KASH[6], T. C. JHOU[7], M. R. BRUCHAS[1,2,3]
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Abstract: Nociceptin/Orphanin FQ Opioid Receptor (NOPR) and its endogenous ligand, nociceptin (NOC) are widely distributed throughout the brain and have been demonstrated to have a role in mediating pain, stress, anxiety, feeding, and reward behaviors. In particular, systemic NOPR stimulation has been shown to inhibit dopamine neuron firing and reduce drug-reward behavior. However, the endogenous sources and natural role of nociceptinergic circuits within these reward behaviors are not understood. Using a novel knockin prepronociceptin (PNOC)-Cre mouse driver line and retrograde tracing techniques, we discovered a population of prepronociceptin neurons located within the paranigral and paraintrafascicular nuclei of the ventral tegmental area (peri-VTA). We found that these prepronociceptin neurons have monosynaptic projections onto dopamine cells and selective ablation of these cells enhanced sucrose seeking under fixed ratio three and progressive ratio operant tasks. In addition, we found that chemogenetic stimulation of peri-VTA nociceptin cells and optogenetic photo-stimulation of peri-VTA prepronociceptin terminals reduced operant responding in the progressive ratio task as well as caused conditioned place aversion. These findings identify a previously unknown population of nociceptin-containing neurons that are positioned to tonically suppress reward motivation via dopamine cell inhibition. To assess the functional activity of this prepronociceptin cell population during fixed and progressive ratio operant tasks, we used fiber photometry to record activity of prepronociceptin neurons during operant behavior. Understanding how this discrete nucleus regulates motivation and reward seeking behaviors could provide critical insight into behaviors dysregulated during motivational states such as depression and addiction.

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Topic: G.02. Motivation

Support: R01DA042499

T32NS007205

Title: Nucleus accumbens mu-opioid receptors are necessary for the enhancement of motivated behaviors

Authors: ***D. C. CASTRO**, A. GUGLIN, T. ONYEADOR, M. R. BRUCHAS
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Abstract: Mu opioid receptors (MORs) are involved in motivation for natural and drug rewards. One site for MOR action is nucleus accumbens medial shell (NAc mShell). MOR stimulation in this mesocorticolimbic hub enhances appetitive behaviors such as food intake and social interactions. By contrast, disruption of MOR signaling has yielded ambiguous results. Here, we sought to determine when mu opioid receptors are recruited to mediate motivated behaviors by disrupting MOR signaling during baseline or enhanced motivated states (i.e., ad libitum versus food deprived, social versus isolated housing). To disrupt MOR signaling, we used constitutive $MOR^{-/-}$ knockout (KO), conditional knockout ($Oprm1^{fl/fl}$), and pharmacological approaches. KOs showed normal baseline behaviors compared to wildtype controls, but failed to show enhanced motivation after food deprivation or social isolation. Targeted viral deletion of MORs in NAc mShell of $Oprm1^{fl/fl}$ mice showed a similar pattern, suggesting that MORs are recruited to enhance, not generate motivated behaviors. Next, to determine whether MORs are dynamically recruited, we microinjected CTAP (MOR antagonist) into NAc mShell. MOR blockade only reduced motivated behaviors when animals were in heightened motivated states. Finally, to pinpoint which neuronal populations are important in NAc mShell for MOR-mediated enhancements, we crossed $Oprm1^{fl/fl}$ mice with dynorphin- or enkephalin-cre mice to delete MORs from those neuronal populations. Results suggest that MORs act primarily via D1/dynorphin neurons, but not D2/enkephalin neurons. Future work will further define the mechanisms mediating MOR control over motivation by testing MOR sufficiency in receptor rescue experiments, by quantifying changes in neural ensemble activity via *in vivo* calcium imaging, and by optically stimulating photosensitive MOR chimeras during discrete,

behaviorally relevant events. These results will show where, how, and when MOR signals act to enhance motivated behaviors.

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Topic: G.02. Motivation

Support: NIH-NIDA Grant 11-PAF05335

Title: DREADD-activation of the mesolimbic circuit alters cue-induced behavior

Authors: *L. FERGUSON[1], L. G. LONGYEAR[2], A. M. AHRENS[2], J. ALDRIDGE[2]
[1]Psychology, [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Rats express differences in their motivation to approach and interact with learned reward-paired cues. Pavlovian conditioning in which an approachable cue (a lever) precedes a reward by a few seconds will expose these individual differences. As rats learn the association of a cue and a paired reward, they diverge into different groups. Some rats approach and interact with the Pavlovian cue when its presented (sign-trackers, STs) while other individuals respond to the cue by moving to and engaging the reward delivery apparatus (goal-trackers, GTs). To investigate neural circuit differences between these individuals, the impact of the ventral pallidal (VP) influence on the ventral tegmental area (VTA) was examined. We have previously shown that firing patterns of ventral tegmental dopamine neurons are more active in STs than GTs to presentation of incentive cues. The VP acts to regulate populations of active VTA dopaminergic neurons and as a result may alter tonic dopamine release in the nucleus accumbens (Floresco et al., 2003). This study utilizes designer receptors exclusively activated by designer drugs (DREADDs) to selectively target neurons projecting from the VP to the VTA and the consequent effects of DREADD-activation on behaviors directed towards Pavlovian cues. By inhibiting the rostral VP during Pavlovian conditioning we expect that incentive salience of reward-paired cues will increase producing more sign-tracking behavior. Animals (n=14) received inhibitory DREADDs targeting VP neurons projecting to the VTA. After a 2-week incubation period, animals were trained in Pavlovian conditioned approach paradigm (PCA) and then tested in the Pavlovian task for an additional 2 weeks with injection of either CNO to activate DREADDs or saline for controls. Immediate behavioral effects due to DREADD activation with CNO were seen only in STs on day 1 of testing, expressed as increasing lever contacts. In contrast, DREADD activation showed changes in goal-trackers over the 5 days of testing. Specifically,

GTs demonstrated increased probability to contact lever, decreased latency to approach lever, increased latency to enter magazine, decreased probability of a magazine entry, and overall fewer magazine entries. In short, GTs exhibited more sign-tracking-like behavior with DREADD evoked activation disinhibiting the VP to VTA circuit and increasing dopamine with concomitant enhancement of incentive salience. A ceiling effect on sign-tracking behavior in STs, on the other hand, may limit changes in that phenotype. Future work will explore correlates of these behavioral shifts to neural firing pattern changes in dopamine and non-dopamine neurons in the VTA.

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Poster

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Topic: G.02. Motivation

Support: MOBILEX DFF – 5053-00215

Title: Motivational regulation by dopamine D2 receptor downstream signaling pathways

Authors: *T. RAHBEK-CLEMMENSEN, E. GALLO, P. DONTHAMSETTI, J. JAVITCH, C. KELLENDONK
Dept. of Psychiatry, Columbia Univ., New York, NY

Abstract: Deficits in motivation are core negative symptoms in several psychiatric disorders. In schizophrenia dopamine D2R receptor (D2R) occupancy in the Nucleus Accumbens (NAc) is inversely correlated with negative symptoms. Using a mouse model with specific, viral-mediated upregulation of D2R in the indirect pathway of NAc core (D2R-OE_{IndAc} mice), we observed increased motivation in a progressive ratio task and locomotor activity as well as increased excitability and decreased excitatory input and output of indirect medium spiny neurons. With the development of two novel D2R mutants that either signal specifically via Gi/o/z or arrestin signaling pathways, we have a unique opportunity to determine which downstream pathways are important for regulating directional and activational components of motivation. Using in vivo studies, we are investigating how the signaling-bias in the medium spiny neurons of the indirect pathway affects the motivated behavior and locomotor activity. In parallel, we examine the effect on the physiological properties and circuitry of these medium spiny neurons to characterize the effect of either of these two mutants on the neuronal excitability and changes in neuronal circuitry and as well as the relationship to our behavioral data. Overall, the project could provide a potential path towards new therapeutic strategies for psychiatric disorders.

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Poster

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Topic: G.02. Motivation

Support: Brain & Behavior Research Foundation NARSAD Award

Title: Nucleus accumbens activity during acquisition, maintenance, and extinction of sign-tracking and goal-tracking behavior

Authors: *Z. S. GILLIS, S. E. MORRISON
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Abstract: Drug-related cues may acquire incentive value, precipitating relapse by making an addict more likely to interact with them. However, there is broad variation among individuals in the power of such reward-predictive cues to control behavior. This variation may be modeled in rodents using a Pavlovian conditioned approach assay in which some subjects tend to interact with the conditioned stimulus (CS) - a behavior known as “sign tracking” - while others tend to approach the site of reward, a behavior known as “goal tracking.” Sign tracking has been found to be more resistant than goal tracking to both reward devaluation (Morrison et al., 2015) and extinction learning (Ahrens et al., 2015). These behavioral differences are paralleled by neurochemical differences in the mesocorticolimbic reward pathway: in sign-trackers, cue-evoked dopamine (DA) release in the nucleus accumbens (NAc) is higher than in goal-trackers, while DA release evoked by the reward becomes lower over the course of training (Flagel et al., 2011). However, the impact of these differences on the signaling of individual neurons in the NAc remains unclear. Therefore, we recorded the activity of single cells in the NAc core in both sign-tracking and goal-tracking individuals during the acquisition, maintenance, and extinction of conditioned approach. Surprisingly, after acquisition, we found little difference in cue-evoked firing between the two behavioral response profiles, and the magnitude of cue-evoked excitations had a strong inverse relationship with latency to perform either action. Moreover, in both sign trackers and goal trackers, we observed firing patterns consistent with negative reward prediction errors at the time of omitted reward. In contrast to these similarities, we found that sign-tracking subjects retained higher cue-evoked firing rates in the NAc during extinction learning, consistent with their behavioral resistance to extinction. Finally, systemic administration of quinpirole, a D2 receptor agonist, reduced baseline activity, cue-evoked excitation, and behavioral responses to the cue in both sign trackers and goal trackers. Future experiments will focus on refining our

understanding of the relationships among DA release, sign-tracking and goal-tracking behavior, and the activity of individual neurons in the NAc.

Disclosures: Z.S. Gillis: None. **S.E. Morrison:** None.

Poster

697. Motivation: Subcortical Neurocircuitry

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Topic: G.02. Motivation

Support: NRSA 1F32DA038942

TNDA 5T32DA024635

R01-DA035443

Title: Cortical-amygdala circuits for value-based decision making

Authors: *M. MALVAEZ[1], C. SHIEH[1], M. MURPHY[1], V. Y. GREENFIELD[1], H. G. MONBOUQUETTE[2], K. M. WASSUM[1]
[1]Psychology, [2]Chem. & Biomolecular Engin., UCLA, Los Angeles, CA

Abstract: The value of an anticipated reward is a major contributing factor in the decision to engage in actions towards its pursuit. Such value is dynamic, fluctuating based on one's current need state, and must be learned through relevant state experience (e.g., consumption of a food item while hungry). The basolateral amygdala (BLA) is required for this incentive learning process, but little is known about how it achieves this function within the broader reward-seeking circuitry and whether it also participates in the online use of reward value during decision making. Because the BLA is densely innervated by cortical glutamatergic projections, we hypothesized that glutamate released into the BLA would track changes in reward value important for value-guided reward seeking. To test this, we used electroenzymatic biosensors to make near-real time measurements of BLA glutamate concentration changes during incentive learning (experience with a food reward in novel hungry state) and a subsequent reward-seeking test. Transient elevations in BLA glutamate concentration were detected that tracked the incentive learning process. No such changes were detected in the absence of incentive learning when the food was experienced in a familiar state. BLA glutamate elevations were also detected immediately preceding bouts of subsequent reward-seeking activity, but only if rats had access to the current value of the food reward. Supporting these correlational data, inactivation of BLA NMDA glutamate receptors prevented incentive learning, while inactivation of either BLA AMPA or NMDA receptors attenuated the normal increase in reward seeking that would occur following a positive incentive learning opportunity. We next used designer receptor-mediated

inactivation of specific glutamatergic cortical projections to the BLA to determine the afferent contributors to these input signals. Projections from the lateral orbitofrontal cortex (OFC) were found to be necessary for encoding a positive change in reward value, but not for later retrieval of this information for online decision making. Conversely, projections from the medial OFC were not required for incentive learning, but their inactivation did disrupt online reward-seeking activity. These data demonstrate that the BLA participates in both the encoding and retrieval reward value via input signals from the lateral and medial OFC, respectively.

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Poster

697. Motivation: Subcortical Neurocircuitry

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Topic: G.02. Motivation

Support: RO1 DA035443

T32 DA024635

R01 NS087494

R01 MH106972

Title: The role of basolateral amygdala output pathways in reward expectation-guided behavior

Authors: ***N. T. LICHTENBERG**[1], Z. T. PENNINGTON[1], V. Y. GREENFIELD[1], K. M. WASSUM[1,2]
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Abstract: Reward-related decisions are heavily influenced by expectations about future potential rewards. These expectations are generated by using information in the environment (e.g. stimuli or available actions) to retrieve detailed memories of associated rewards. The basolateral amygdala (BLA) is a key node in the circuitry supporting expectation-guided behaviors, but little is known about how specific BLA outputs contribute to this function. The BLA sends excitatory projections to several cortical and striatal regions, including the orbitofrontal cortex (OFC) and dorsomedial striatum (DMS), which are independently implicated in reward expectation-guided behaviors. We used designer receptor-mediated inactivation of specific BLA output pathways to evaluate their contributions to expectation-guided behaviors. Pathway-specific chemogenetic inactivation of monosynaptic BLA to OFC projections disrupted the motivating influence of cue-triggered reward expectations over action selection and conditioned goal-approach responding as

assayed by outcome-specific Pavlovian-to-instrumental transfer (PIT) and Pavlovian devaluation, respectively. These projections were not necessary when actions were guided by reward expectations generated based on learned action-reward contingencies, or when rewards were physically present to direct responding. These data suggest that bottom-up projections from the BLA to the OFC enable cue-triggered expectations to guide adaptive conditioned responding and decision making. Ongoing experiments are evaluating the contribution of BLA to DMS projections in reward expectation-guided conditioned responding and action selection.

Disclosures: **N.T. Lichtenberg:** None. **Z.T. Pennington:** None. **V.Y. Greenfield:** None. **K.M. Wassum:** None.

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Topic: G.02. Motivation

Title: A novel viral approach for genetically targeting ventral tegmental area GABA projection neurons in wildtype rats reveal heterogeneous terminal fields throughout the cortex, subcortical and mesolimbic regions

Authors: ***M. FEJA**[1], A. SHIELDS[1], K. T. WAKABAYASHI[1,2], A. VENNER[3], P. M. FULLER[4], C. E. BASS[1]
[1]Univ. At Buffalo SUNY, Buffalo, NY; [2]Res. Inst. On Addictions / Univ. At Buffalo, Buffalo, NY; [3]Dept. of Neurol., [4]Harvard Med. Sch., Boston, MA

Abstract: Genetic manipulation techniques have been useful in elucidating the function of defined neuronal subtypes. However, their lack of specificity in non-murine models limits their translational applicability, particularly in behavioral models that primarily use rats. We have recently developed a dual adeno-associated virus (AAV) targeting system to restrict expression of transgenes to dopamine neurons in both wildtype rats and mice. In this system, one AAV delivers Cre recombinase under the control of subtype specific promoter (e.g. tyrosine hydroxylase), while another virus delivers a Cre dependent construct (e.g. DIO, FLEX cassettes) under a strong generalized promoter (e.g. EF1α, or hSyn). Only in neurons where these two constructs overlap does expression occur. Recently, we have developed a new Cre virus under the control of the gamma-amino decarboxylase 1 (GAD1) promoter. By co-infusing GAD1-Cre-AAV2/10 with EF1α-DIO-hM3D-mCherry-AAV2/10 into the ventral tegmental area (VTA), we have been able to target hM3D, the activating designer receptor exclusively activated by designer drugs (DREADD), to GABA neurons in this region. In addition to the strong mCherry expression in the VTA, there were distinct and intense terminal fields throughout the brain. Most GABA neurons in the VTA are interneurons, but ~1 in 5 are GABA projection neurons (GPNs)

that send efferents to multiple brain regions. We observed extensive projections to the striatum, in both dorsal and ventral subregions. In particular, there was a distinct dorsolateral to dorsomedial gradient. In the ventral striatum, there was intense terminals in the olfactory tubercle and nucleus accumbens (NAc), with the core receiving more dense projections relative to the shell. We also observed moderate expression of VTA GABA terminals in the ventral pallidum and medial prefrontal cortex (mPFC), particularly in the anterior cingulate and prelimbic cortex, among other regions. To target the VTA GPNs to the NAc we infused GAD1-Cre-AAV2/6 into this region, and the EF1α-DIO-hM3D-mCherry-AAV2/10 into the VTA. AAV2/10 transduces cells bodies at the injection site, while AAV2/6 is also retrogradely transported, allowing us to transduce only those GAD1+ neurons in the VTA that project to the NAc. We observed extensive mCherry+ cell bodies within the VTA and terminals primarily within the NAc core and to a lesser extent in the shell. Intriguingly, GABAergic signals were also found in several other regions, including the dorsomedial striatum, prefrontal cortex, and olfactory tubercle, suggesting the existence of GPN collaterals arising from the VTA to NAc projections.

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Poster

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Topic: G.02. Motivation

Support: Stanford NeuroChoice Initiative

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FINRA Investor Education Foundation

Title: White-matter tract connecting amygdala and nucleus accumbens is associated with probabilistic reward learning

Authors: ***J. K. LEONG**[1], G. R. SAMANEZ-LARKIN[2], B. KNUTSON[1]
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Abstract: Amygdala and nucleus accumbens (NAcc) circuits may contribute to dissociable aspects of reward seeking. While previous research has shown that NAcc activity can precede and predict reward seeking, recent work suggests that glutamatergic projections from the basolateral amygdala to the NAcc can also promote reward seeking behaviors. However, less research has examined the white-matter tracts that connect these circuits. White-matter tracts

conduct neural signals between circuits, and thus may mediate the effect of one circuit on the other. To study the potential relevance of a putative amygdala-NAcc tract to probabilistic reward learning in humans, we conducted an experiment in which individuals first performed a monetary incentive learning task, followed by a diffusion-weighted MRI scan. In the learning task, individuals chose between pairs of fractal cues and learned to select the better cue to maximize earnings. Individuals selected between cue pairs in gain, loss, and neutral conditions. In the gain cue pair, one cue represented a higher probability of monetary gain (66% +$1.00 / 33% +$0.00 versus 33% +$1.00 / 66% +$0.00). In the loss cue pair, one cue represented a higher probability of avoiding loss (66% -$0.00 / 33% -$1.00 versus 33% -$0.00 / 66% -$1.00). In the neutral cue pair, both cues represented no monetary outcome (100% $0.00). Behaviorally, learning performance for gain acquisition and loss avoidance were uncorrelated ($r = -0.31$, $t(17) = -1.32$, $p = 0.20$). In the same sample, we additionally performed probabilistic tractography on diffusion-weighted MRI data to trace tracts connecting the amygdala and the NAcc. Tractography results revealed the amygdala-NAcc tract follows the ventral amygdalofugal pathway, leaving the temporal lobe with the uncinate fasciculus but then diverging medially to terminate in the posterior NAcc. Coherence of this tract was then estimated by calculating fractional anistropy along the tract and averaging across the middle 50% of the tract. Individual differences in coherence of the amgydala-NAcc tract was positively associated with successful probabilistic reward learning in both gain acquisition and loss avoidance domains, however the effect was driven by gain learning (both: $r = 0.52$, $t(17) = 2.50$, $p = 0.02$; gain: $r = 0.46$, $t(17) = 2.11$, $p = 0.05$; loss, $r = 0.10$, $t(17) = 0.41$, $p = 0.69$). Our results extend previous research suggesting that white-matter tracts projecting to the NAcc can facilitate probabilistic reward learning, and implicate input from amygdala to NAcc in forming associations between novel cues and reward outcomes.

Disclosures: **J.K. Leong:** None. **G.R. Samanez-Larkin:** None. **B. Knutson:** None.

Poster

697. Motivation: Subcortical Neurocircuitry

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 697.22/OO9

Topic: G.02. Motivation

Support: NSERC

CIHR

Title: Effects of optogenetic stimulation of DRN 5-HT neurons and 5-HT input to the mesolimbic DA system on operant responding for a primary reinforcer

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Abstract: Serotonin (5-hydroxytryptamine; 5-HT) neurons originating in the midbrain raphe nuclei innervate virtually the entire brain and are implicated in the control of many behavioural processes. Several lines of evidence suggest that serotonin exerts an inhibitory influence over motivated behaviour, but it is uncertain what 5-HT pathways mediate this effect. Serotonin neurons originating in the dorsal raphe nucleus (DRN) have been implicated in reward processing and reward-related behaviour. These neurons also heavily innervate the mesolimbic dopamine (DA) system – a critical neural substrate for motivation. The DRN sends particularly dense input to the ventral tegmental area (VTA), which could enable 5-HT to regulate mesolimbic DA output. In these experiments, we used an optogenetic approach to identify the role of the DRN-VTA pathway in modulating incentive motivation. The optogenetic construct was developed by crossing mice from the serotonergic cre-driver line ePet-Cre with Ai32 mice, which bear a ubiquitous conditional ChR2-EYFP allele downstream of a loxP-flanked STOP cassette. The progeny of this cross express ChR2 exclusively in 5-HT neurons. Mice received stereotaxic implantation of an optical fiber targeting either the DRN or VTA. First, we tested whether optogenetic stimulation of DRN 5-HT neurons altered lever pressing for the primary reinforcer saccharin (0.2%, 0.02 ml) on a RR4 schedule of reinforcement. Photostimulation (10 mW, 10 ms pulses) of the DRN had no effect on responding for saccharin at a range of frequencies (1, 5, 10, 20 Hz). However, when DRN photostimulation (2.5 Hz) was coupled with the selective 5-HT reuptake inhibitor citalopram (5 mg/kg), a synergistic reduction in responding for saccharin was observed. Analysis of within-session responding found that combining DRN photostimulation with citalopram dramatically reduces responding early in testing. Next, we examined the effects of optogenetic stimulation of 5-HT input to the VTA on responding for saccharin. Photostimulation (5 mW, 10 ms pulses) of 5-HT terminals in the VTA alone had no effect on responding for saccharin, but combining photostimulation with citalopram treatment (5 mg/kg) greatly reduced responding, particularly early in the test session. Together, these results support an inhibitory function of DRN 5-HT neurons in modulating motivation and suggest that this may be mediated in part by 5-HT input to the VTA. Further, the ability of 5-HT to alter incentive motivation in this pathway appears to depend critically on the regulation of extracellular 5-HT by the serotonin transporter.

Disclosures: C.J. Browne: None. **X. Ji:** None. **Z. Li:** None. **P.J. Fletcher:** None.

Poster

698. Emotional States: Anxiety and Pain

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Howard Hughes Medical Institute

NIH NIDA DA031777

Rita Allen Foundation and American Pain Society Award in Pain

Title: Amygdalar neural ensembles that encode the aversive quality of pain experience

Authors: *G. F. CORDER[1], B. AHANONU[2], B. GREWE[5], M. SCHNITZER[3], G. SCHERRER[4]
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Abstract: The experience of pain leads to motivated behaviors that limit exposure to noxious stimuli. However, it remains unknown how the brain's affective neural circuits generate the aversive quality of pain. To identify a neural basis for pain aversion, we used chemogenetic and in vivo calcium imaging methods to study nociceptive neural ensembles in the basal and lateral amygdala (BLA) of mice. By using a head-mounted miniature microscope to track the dynamics of these cells in freely behaving mice, we identified BLA neural populations that represent different types of painful stimuli via a combinatorial coding scheme. Chemogenetic silencing of nociceptive cell ensembles selectively alleviated pain affective-motivational behaviors, but without affecting detection of noxious stimuli, withdrawal reflexes, anxiety levels or reward seeking. After induction of a neuropathic pain state, innocuous stimuli prompted heightened activation of the nociceptive cell ensembles. Remarkably, silencing neuropathic cell ensembles blocked the pathological affective dysfunctions that characterize chronic pain. Collectively, these results indicate there is a neural representation of nociception in the amygdala that is functionally required for the innate, negative quality of painful experiences.

Disclosures: G.F. Corder: None. **B. Ahanonu:** None. **B. Grewe:** None. **M. Schnitzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inscopix. **G. Scherrer:** None.

Poster

698. Emotional States: Anxiety and Pain

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Title: A new monosynaptic craniofacial affective pain neural circuit drives robust aversive behaviors

Authors: *E. RODRIGUEZ[1], K. SAKURAI[1], J. XU[1], D. RYU[1], S. ZHAO[1], K. TODA[2], H. H. YIN[2], B. HAN[1], F. WANG[1]
[1]Neurobio., [2]Psychology and Neurosci., Duke Univ., Durham, NC

Abstract: Humans often rank craniofacial pain as more severe than body pain. Evidence suggests that a stimulus of the same intensity induces more pain in the face than the body. However, the underlying neural circuitry for the differential processing of facial versus body pain remains unknown. Interestingly, the lateral parabrachial nucleus (PB_L), a critical node in the affective pain circuit, is activated more strongly by noxious stimulation of the face than the hind paw. Using a novel activity-dependent technology called CANE developed in our lab, we identified and selectively labeled pain-activated PB_L neurons, and performed comprehensive anatomical input-output mapping. Surprisingly, a hitherto uncharacterized monosynaptic connection specifically between cranial sensory neurons and the PB_L-pain neurons was discovered. Optogenetic activation of this monosynaptic craniofacial-to-PB_L projection induced robust escape/avoidance behaviors and stress calls. The new circuit route revealed here thus provides a neural substrate for heightened craniofacial affective pain.

Disclosures: E. Rodriguez: None. **K. Sakurai:** None. **J. Xu:** None. **D. Ryu:** None. **S. Zhao:** None. **K. Toda:** None. **H.H. Yin:** None. **B. Han:** None. **F. Wang:** None.

Poster

698. Emotional States: Anxiety and Pain

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Topic: G.03. Emotion

Support: MEXT-Supported Program for the Strategic Reserch Foundation at Private Universities

Title: Distinct time course of the limbic activation between spinal and trigeminal inflammatory pain models as revealed with manganese enhanced MRI in the mouse

Authors: *F. KATO[1], D. ARIMURA[1], Y. TAKAHASHI[1], K. SHINOHARA[2], T. TSURUGIZAWA[3], T. TOKITA[1], R. IKEDA[2], K. MARUMO[2]

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Abstract: Recent functional brain imaging studies in human subjects indicate that a shift of brain regions that are spontaneously activated characterizes the process from acute-to-chronic pain transition. In particular, the activation of the limbic system is proposed to be a hallmark of the establishment of chronic pain. In agreement with this notion, synaptic activation and phosphorylated ERK expression appearing after the acute pain in the central amygdala have been documented in the rodent model of early inflammatory pain (Carrasquillo & Gereau, 2007; Miyazawa et al., 2014). However, it remains entirely unknown whether such shift of spontaneous pain-associated brain regions also occurs in the animal model of chronic pain. To address this issue, we used manganese (Mn^{2+}) enhanced MRI (MEMRI) with ultra-high field scanner and cryodetectors (9.4T; Bruker Biospec) to visualize the neuronal excitation history in the animals spent under spontaneous behaviors after formalin injection, a model recently shown to show a rapid shift in symptoms from acute pain-like to chronic pain-like. In particular, as the nociception in the areas with spinal and trigeminal innervations is sent to the brain via distinct pathways, effects of the inflammation site on the brain activation pattern were examined by administering formalin to the left upper lip (trigeminal inflammation group; TI) or the plantar (spinal inflammation group; SI) of the left hind paw of the mice at 2 h (scanning after the acute phase; “acute scanning”) or 6 h (that after the acute and post-acute phases; “post-acute scanning”) before the MRI scanning and we compared the accumulation of Mn2+ between groups and treatments. $MnCl_2$ injection and scanning were done at a 22-h interval under isoflurane anesthesia. Except for these and formalin/saline injection, the mice were kept in the home cage and allowed to move freely to ensure spontaneously pain sensation. All mice showed typical acute nocifensive behaviors that faded within <60 min. In post-acute scanning in SI group, and in acute scanning in TI group, a significantly larger accumulation of Mn^{2+} in limbic areas such as the central amygdala was observed. A significant Mn2+ accumulation in the sensory cortex was observed in acute scanning in both groups with distinct somatotopy-dependent patterns. These results indicate a dynamic shift in brain areas presumably associated with spontaneous pain sensation in the acute-to-chronic transition in a manner temporally dependent on the site of inflammation.

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Poster

698. Emotional States: Anxiety and Pain

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Title: Ketamine attenuates the aversive effects of chronic pain

Authors: *H. ZHOU, K. LIU, J. WANG
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Abstract: It is well understood that chronic pain can induce a generalized enhancement in the aversive response to nociceptive inputs, as demonstrated by our previous studies in rodents as well as conditions such as fibromyalgia and persistent postoperative pain. However, effective treatment of these types of conditions has traditionally been difficult, and new therapeutic modalities are urgently needed. In the current study, we ask the following question: Can any pharmacological treatments attenuate this generalized enhancement of pain aversion? We hypothesize that Ketamine, which has recently been shown to provide enduring anti-depressant and anxiolytic properties, may attenuate these aversive effects in the chronic inflammatory pain model.
Complete Freund's Adjuvant (CFA) was injected into the plantar aspect of one hindpaw to induce chronic inflammatory pain. Two days after CFA injection, ketamine (10mg/kg) (or saline control) was administered systemically via intraperitoneal injections. A brief two-chamber conditioned place aversion test (CPA) was performed to quantify the aversive effect of painful stimuli (pin prick). A higher CPA score corresponds to greater aversion of pain-associated chamber. Mechanical allodynia and traditional Hargreaves test were used to measure mechanical and thermal hypersensitivity as an assessment of the sensory component of pain.
Our results show that in the chronic inflammatory pain model, Ketamine is able to significantly attenuate the aversive effects of nociceptive inputs up to five days after treatment. Interestingly, this decrease in aversion is not associated with any change to the sensory component of pain. Our experiments show that Ketamine may represent a novel treatment option for the affective symptoms of chronic pain.

Disclosures: H. Zhou: None. **K. Liu:** None. **J. Wang:** None.

Poster

698. Emotional States: Anxiety and Pain

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Title: Aversive emotional circuits are impaired in the MeCP2^{Tg} mouse

Authors: *B. YU[1], L. HE[2], T. CHENG[1], B. YUAN[1], R. ZHANG[1], Z. QIU[1]
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Abstract: MeCP2 is a DNA binding protein encoded by a gene located on chromosome Xq28 in humans, and is a protein that is evolutionarily conserved both in structure and in function. Large amount of studies have showed that MeCP2 expression level is extremely important for normal function of central nervous system. A loss of function of MeCP2 gene is the main cause of most cases of Rett syndrome, a severe neurodevelopmental disorder. And a gain of function of MeCP2 will cause MeCP2 duplication syndrome, another neurological developmental disease. Both of these syndromes show typical autistic symptoms. In contrast to Rett syndrome, research on MeCP2 duplication syndrome is relatively fewer. Especially, how MeCP2 affects neural circuits in the whole brain is largely unknown. In this study, we used neurotropic viruses tracing method, optogenetic and electrophysiological strategies to target social and anxiety relevant neural circuits in the MeCP2 duplication mouse. We found that BLA-mPFC circuit which is one of the most widely studied aversive emotional circuits is impaired in the MeCP2Tg mice.

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Poster

698. Emotional States: Anxiety and Pain

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Title: Neural signaling in the basolateral amygdala during anxiety

Authors: *G. MAN, J. POPOVITZ, H. ADWANIKAR
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Abstract: Anxiety behaviors form a part of the natural repertoire of animal behavior, with their disorders being a prevalent psychiatric condition. However, the specific neural signaling patterns underlying anxiety remain unclear. Several elements of the corticolimbic circuit, including the amygdala, are strongly implicated in regulating anxiety. Here, using calcium imaging, we record the activity of neurons within the basolateral amygdala over time in mice engaged in anxiety-like

behaviors, and characterize the underlying neural encoding patterns. Results will shed important light on the neural information processing during expression of anxiety-like behavior.

Disclosures: G. Man: None. **J. Popovitz:** None. **H. Adwanikar:** None.

Poster

698. Emotional States: Anxiety and Pain

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Title: Differential activation of arginine-vasopressin receptor subtypes in the amygdaloid modulation of anxiety in the rat by arginine-vasopressin

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Abstract: The amygdala plays a paramount role in the modulation of anxiety and social behaviours. A relationship between arginine vasopressin (AVP), anxiety and aggression has now been suggested. And that both behaviors have as substrate to the amygdala. Numerous studies have shown AVP elicits anxiogenic effects following either its systemic or septal administration. The aim of this study was to evaluated the involvement of vasopressinergic neurotransmission in the amygdaloid modulation of unconditioned anxiety and to ascertain whether or not AVP receptor subtypes may have a differential role in this modulation and if this relationship is involmented in social behaviours. Anxiety behavior was evaluated both in Shock-Probe Burying Test and Light-Dark Box and social behaviour in social interaction test following the bilateral micro-infusion of AVP alone or AVP together with either AVP 1a or AVP 1b receptor antagonists into the central amygdala (CeA) and the social behaviour was evaluated in the social interaction test. AVP micro-infusion elicited at low (1ng/side) but not at high doses (10 ng/side) anxiogenic-like responses in the Shock-Probe Burying Test but not in the Light-Dark Box. SSR149415, an AVP 1b antagonist unlike Manning compound, an AVP 1a antagonist fully prevented AVP effects in the Shock-Probe Burying Test when it was administered together with AVP. No effects of any AVP antagonist by itself were observed in both anxiety paradigms. Moreover, AVP micro-infusion (1ng/side) decreased social behaviors and increased aggression.

Our results indicate that AVP 1b receptor contribute to the amygdaloid modulation of anxiety and social behaviours. It remains to the future to ascertain whether AVP receptor subtypes have indeed differential actions in the modulation of specific features of unconditioned anxiety.

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Poster

698. Emotional States: Anxiety and Pain

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Title: Anxiety cells in a hippocampal-hypothalamic circuit

Authors: *J. C. JIMENEZ[1], K. SU[2], A. GOLDBERG[2], V. LUNA[2], P. ZHOU[2], G. ORDEK[3], S. ONG[2], L. ZWEIFEL[5], L. PANINSKI[2], R. HEN[4], M. KHEIRBEK[6]
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Abstract: The ventral hippocampus (vHPC) may modulate anxiety-related behaviors by connecting cognitive association regions with subcortical structures that can directly impact mood. However, what stimuli are encoded within vHPC circuits and how those representations are used to guide behavior remains unknown. To understand this, we used cell-type specific calcium imaging to investigate how innately anxiogenic contexts are represented in ventral CA1 (vCA1) pyramidal neurons. We found that vCA1, but not dorsal CA1 activity increased during exploration of innately anxiogenic environments. Moreover, the magnitude of this activity increase was tightly correlated with the anxiety state of individual animals. Using a closed-loop

optogenetic design, we found that silencing vCA1 during exploration of anxiogenic environments significantly reduced avoidance behavior, suggesting that vCA1 anxiogenic representations were causally modulating anxiety behavior. We next determined through which vCA1 output streams these effects could be mediated. We focused on vCA1 projections to two subcortical nuclei implicated in anxiety, fear, and behavioral responses to stress, the Basal Amygdala (BA) and Lateral Hypothalamus (LHA). Retrograde tracing studies revealed that vCA1 outputs to the LHA and BA are segregated into two largely non-overlapping cell populations within vCA1. Using optogenetic techniques to control these two vCA1 outputs, we found that modulation of vCA1-LHA, but not vCA1-BA terminals impacts innate anxiety and aversion, while vCA1-BA but not vCA1-LHA terminal modulation impacts contextual fear memory. Finally, we conducted projection-specific calcium imaging to visualize the activity of vCA1-BA and vCA1-LHA neurons during exploration of anxiogenic environments, and found that vCA1-LHA projecting neurons were highly enriched in anxiety-responsive neurons relative to vCA1-BA neurons. This study provides a functional map of the cell-types and long-range circuits that underlie the vHPC contribution to innate anxiety-related behavior, and suggests that the vCA1-LHA pathway may serve as a direct route by which vCA1 can modulate innate avoidance behavior.

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Poster

698. Emotional States: Anxiety and Pain

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CNPQ/PIBIC

Title: Opposite effects produced by N-methyl-D-aspartate (NMDA) receptor activation within the left or right medial prefrontal cortex on anxiety in mice

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Abstract: The medial Prefrontal Cortex (mPFC) is densely populated by glutamatergic neurons, which, in turn, play a role in the modulation of anxiety via NMDA receptor activation. Besides, recent findings have shown that chemical manipulations of the Right (R) or Left (L) mPFC provoke distinct effects on anxiety of mice exposed to the elevated plus maze (EPM). Here, we investigated the effects of NMDA activation in the L or R mPFC on anxiety-like responses of mice exposed to the EPM. Methods: Male Swiss mice (n=5-7) received intra-mPFC injection of saline or NMDA (Right: 0.02 or 0.04 nmol/0.2 µL; Left: 0.04 nmol/0.2 µL). Ten minutes later, each mouse was exposed to the EPM to record the conventional measures of anxiety (percentage of open-arm entries and percentage of open-arm time: %OE and %OT), locomotor activity (frequency of closed-arm entries: CE), risk-assessment behaviors [protected (p) and unprotected (u) stretched attend posture: SAP] and frequency of rearing for a period of 5 minutes. Results: Statistical analysis (R: One-way ANOVA; L: Non-parametric Mann-Whitney test) showed that NMDA differently alter behavior when injected into the R or L mPFC. Intra-RmPFC NMDA injections provoked an anxiogenic-like effect [%OE: $F(2,13)= 4.14$; %OT: $F(2,13)= 13.94$; $p<0.05$] without changing CE [$F(2,13)= 0.37$; $p>0.05$]. In contrast, intra-LmPFC NMDA injection provoked a borderline anxiolytic-like effect, increasing open-arm exploration (%OE: $Z=1.70$; $p=0.08$; %OT: $Z=1.86$ $p=0.06$) without changing locomotor activity [CE: $Z=0.89$; $p=0.3$]. Also, Left-NMDA treatment tended to reduce the pSAP ($Z=1.70$; $p=0.08$) without changing the uSAP ($Z=-0.81$; $p=0.41$), whilst activation of the RmPFC did not alter the pSAP [$F(2,13)=0.52$; $p=0.6$] but reduced the uSAP [$F(2,13)=3.09$; $p=0.04$ at 0.02 nmol dose]. Neither R nor L treatment alter frequency of rearing [L: $Z=-0.56$; $p=0.56$; R: $F(2,13)=4.03$; $p>0.13$], suggesting NMDA effects were selectively on anxiety-related behaviors. Conclusion: These results are suggestive that glutamate NMDA receptors located within the RmPFC and LmPFC play an anxiogenic- and anxiolytic-like role in the modulation of anxiety in mice exposed to the EPM.

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Poster

698. Emotional States: Anxiety and Pain

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Topic: G.03. Emotion

Support: CAPES/PROEX

CNPq

Title: Carbon monoxide promoted anxiolytic-like effect and increasing expression of heme-oxigenase in locus coeruleus

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Abstract: Previous study suggested that the carbon monoxyde (CO) acting on locus coeruleus (LC) play role on emotional behavior modulation. Again, the LC has high expression of the heme-oxygenase (HO) enzyme, responsible for the production of CO. The CO in LC can modulate the activity of the local neurons, however, the mechanism by which the HO-CO pathway of LC participates in the modulation of emotional responses needs to be elucidated. Here, we investigate whether the systemic treatment (ip) acute (3h before) or chronic (10 days/2 times a day) with a carbon monoxide releaser (CORM-2) or an inducer of heme enzyme oxygenase (CoPP), is able to alter the behavioral responses in the elevated plus maze (EPM) and in the light-dark box test (LDB), and the expression of the HO-1 or HO-2 enzymes into LC cells in rats. Male Wistar rats (200g, n=50, CEUA 2015.1.531.58.4) were divided into distinct groups that received acute or chronic treatment with CORM-2 (5mg/kg, i.p.), CoPP (2.5 mg/kg, i.p.) or vehicle (DMSO) and were submitted to EPM and LDB for 5 min each test. Two-way ANOVA was used for the analysis followed by the Tukey test ($P<0.05$). The results showed that the CO induced by acute or chronic administration of CORM-2 or CoPP increased the number of entries into the open arms and the percentage of time spent in the open arms in the EPM when compared to control group ($P<0.05$). In the LDB test, chronic treatment with both drugs increased the time spent in the light compartment compared to control group ($P<0.05$). The treatment with CORM-2 or CoPP (acute and chronic) promoted an increase HO-1 enzyme expression in cells located in the LC without altering the immunoreactivity of HO-2 enzyme. These results shown that the CO promoted anxiolytic-like effect and increasing expression of HO-1 enzymes in LC cells.
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Poster

698. Emotional States: Anxiety and Pain

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DA041482

Title: Control of anxiety-like behavior by serotonergic circuits innervating the interpeduncular nucleus

Authors: *I.-J. YOU[1], L. LIU[1], A. SACINO[1], M. UCHIGASHIMA[1,2], K. FUTAI[1], A. R. TAPPER[1]
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Abstract: Recently, the interpeduncular nucleus (IPN) has been implicated as a critical neuroanatomical substrate for modulating fear and anxiety-like behavior. However, functional IPN afferent and efferent circuitry that contributes to these behaviors is largely unknown. Interestingly, viral tracing studies indicate that the IPN receives projections from the medial raphe nucleus (MRN), although serotonergic signaling in the IPN and the functional relevance of this MRN→IPN input has not been elucidated. Molecular and biophysical analysis of 5-HT receptors in the IPN indicated robust functional expression of 5-HT1, but not 5-HT5 receptors. Double fluorescent in situ hybridization experiments revealed co-localization of 5-HT1A receptor and glutamic acid decarboxylase 67 transcripts suggesting serotonergic IPN inputs innervate GABAergic neurons in the rostral sub-nuclei of the IPN. To test the hypothesis that MRN→IPN serotonergic inputs modulate anxiety-like behavior, we expressed channelrhodopsin in MRN serotonergic neurons that project to the IPN using retrograde viral delivery in FEV-Cre mice. Optical stimulation of serotonergic terminals in the IPN increased anxiety-like behavior in the elevated plus maze and open field test. In contrast, stimulation of MRN→IPN inputs did not significantly affect locomotor activity, depression-like behavior, or reward. These results reveal a novel role for a serotonergic MRN→IPN circuit in modulating anxiety-like behavior.

Disclosures: I. You: None. **L. Liu:** None. **A. Sacino:** None. **M. Uchigashima:** None. **K. Futai:** None. **A.R. Tapper:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.12/OO21

Topic: G.03. Emotion

Support: KAKENHI 15K12767

KAKENHI 24227001

Title: Molecular mechanism of circadian regulation of mouse anxiety-like behavior

Authors: *K. SHIMIZU, J. NAKANO, Y. FUKADA
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Abstract: Circadian regulation of physiology extends to higher brain functions including cognition and memory, such that time-of-day-dependent variations in cognitive performance and

memory formation have been described in various species. Disturbances in human activity rhythms such as those arising from rotating shift work or jet lag increase the risk for mood disorders. In rodents, perturbations of the circadian clock by means of surgical, genetic, pharmacological or light-induced manipulations lead to a spectrum of abnormalities in emotionality-related behaviors, including elevated or attenuated anxiety-like behaviors. While these lines of evidence show that disruption of the circadian clock triggers a spectrum of affective abnormalities, how the clock regulates mammalian emotionality remains unclear. We sought to unravel the mechanisms governing mammalian anxiety regulation and characterized temporal regulation of mouse anxiety-like behaviors by the circadian clock. We show that anxiety-like behaviors are expressed in a circadian manner in mice and demonstrate that the clock machinery in the dorsal telencephalon is required for the time-of-day-dependent regulation of anxiety-like behaviors. We identify SCOP/PHLPP1β (suprachiasmatic nucleus circadian oscillatory protein) as an essential intracellular signaling molecule mediating this temporal regulation downstream of the clock. SCOP is a signaling molecule originally identified as a gene product whose expression oscillates in a circadian manner in the rat SCN (Shimizu *et al*. FEBS Lett 1999). SCOP protein is predominantly expressed in the central nervous system, and has been shown to regulate a range of intracellular signaling pathways (Shimizu *et al.* Cell, 2007). Using viral-mediated, basolateral amygdala (BLA)-specific knockout of *Scop*, we demonstrate that deletion of SCOP in the BLA exerts anxiolytic effects on the elevated plus maze at early subjective night, thereby blunting the circadian variation in the anxiety-like behavior. We conclude that the circadian expression of SCOP in the BLA plays a key role in generating circadian rhythmicity in the anxiety-like behavior. Our results demonstrate SCOP as a regulator of anxiety-like behaviors and reveal its key role in the anxiogenic functions of the BLA. (Nakano *et al*. Sci Rep, 2016)

Disclosures: K. Shimizu: None. **J. Nakano:** None. **Y. Fukada:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.13/OO22

Topic: G.03. Emotion

Title: Efficacy of voluntary exercise in reducing anxiety in female mice

Authors: *C. NEELY[1], L. ROSARIO[2], A. SANCHEZ[2], B. ADAMS[2], J. FLINN[1]
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Abstract: Women experience anxiety at a higher rate than men, and strategies that benefit men may not generalize across gender. We sought to explore the effect of exercise on anxiety in

female mice as an analogue for women. Mice *(N*=16) were housed in two conditions: one with a running wheel and one with a standard PVC pipe as enrichment. Data were collected via the elevated zero maze following 27 days of housing conditions. Prior to data collection, we hypothesized that access to a running wheel in the homecage would reduce anxiety-like behaviors in comparison to standard housing. Data did not violate the assumption of equal variances; therefore, we conducted a one-sided independent samples *t*-test to analyze the beneficial effects of the presence of a running wheel on percentage of time spent in the open arms and risk-assessment behaviors in the EZM. Mice with running wheels spent more time in the open arms of the maze (21.2 ± 10%) compared to mice without running wheels (15.2 ± 11.6%); however this difference was not significant, $t(14) = 1.11$, $p = 0.14$. Mice with running wheels also exhibited more head-dips in the open arms (22 ± 5.4) compared to mice without running wheels (15.8 ± 8.2). This difference in risk-assessment behavior was significant, $t(14) = 1.80$, $p = 0.05$. This study showed decreases in anxiety because of an available running wheel in the homecage. This study is currently being replicated with larger sample sizes, male mice, and additional behavioral tests. Overall, results show that exercise may be a promising research topic for anxiety treatments oriented towards women.

Disclosures: C. Neely: None. **L. Rosario:** None. **A. Sanchez:** None. **B. Adams:** None. **J. Flinn:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

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Program#/Poster#: 698.14/OO23

Topic: G.03. Emotion

Title: Candidate anxiolytic drug testing in human approach-avoidance anxiety: Comparison of lorazepam, pregabalin, and valproate

Authors: *D. R. BACH, C. W. KORN, A. BANTEL, J. VUNDER
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Abstract: Preclinical screening of potential anxiolytic substances in non-human animals relies on the premise that the neurochemistry of anxiety is sufficiently conserved across species. Some anticonvulsant drugs with strong preclinical evidence for acutely anxiolytic properties in rodents, such as valproate, have not been translated to clinical application, urging cross-species investigation. Here, we capitalised on a recently developed human anxiety test emulating rodent approach-avoidance conflict such as elevated plus maze (EPM), open field, or operant conflict. Our "stay and play" test has been shown sensitive to the impact of the GABAergic anxiolytic lorazepam, and of both hippocampal and amygdala lesions. In a double-blind, randomised, placebo-controlled trial, participants played a computer game while under the established

GABAergic anxiolytic pregabaline (200 mg), the candidate anxiolytic valproate (400 mg), or placebo. Primary outcome measure (presence in safe place) and a priori contrast (linear drug x intra-epoch time adaptation) were chosen based on a previous study with 1 mg lorazepam. Peak saccadic velocity and subjective ratings were assessed as control measures for drug-induced sedation. Both valproate and pregabaline were anxiolytic in the primary and several secondary outcome measures. Bayesian model comparison indicated no differences between the two drugs. Subjective and objective sedation was significantly more pronounced under pregabalin than valproate, but did not explain anxiolytic effects. In comparison, 1 mg lorazepam had a stronger anxiolytic effect than the drug doses used here. In summary, our results suggest a potential use of valproate as anxiolytic drug. More generally, we propose a strategy of screening drugs in human preclinical models that can directly be compared across species, such as the approach/avoidance computer game used here. This approach could thus facilitate translational anxiety research.

Disclosures: D.R. Bach: None. **C.W. Korn:** None. **A. Bantel:** None. **J. Vunder:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.15/OO24

Topic: G.03. Emotion

Title: Neural correlates of subjective pleasure and displeasure in nociceptive pain

Authors: *V. RIMEIKYTE[1], J. L. WHITLOCK[2], A. K. ANDERSON[1]
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Abstract: Nociceptive pain signals damage to body tissue and thus avoiding it is paramount to survival. In line with this function, nociceptive pain is commonly considered inherently aversive. However, despite the aversive qualities of nociceptive pain, some people intentionally and repeatedly engage in self-harming behaviors. In addition, prior research suggests that subjective pain experience can be pleasurable in certain contexts as well as during experience of pain relief. These findings indicate that there may be appetitive components to pain in addition to its aversive qualities. In current study, we aimed to disentangle pleasure and displeasure components of pain experience. Healthy young adult participants (N=10) experienced painful pressure to their thumbs [3-7 kg/cm^2] for 8-11s while undergoing an fMRI scan. After each trial, participants rated pleasant and unpleasant their experience was on a given trial. In our sample, pleasure ratings were only mildly negatively correlated (r = -.32) allowing us to examine the neural activity associated with each component during pain stimulation. Activity in supplementary motor and premotor areas, as well as in inferior parietal lobule scaled with both pleasure and displeasure ratings. Activity in dorsal and posterior cingulate cortices, as well as precuneus and hippocampus, scaled only with displeasure ratings. In addition, displeasure ratings

were correlated with activity in areas associated with self-regulation dorsolateral prefrontal cortex, thalamus, and dorsal striatum (caudate/putamen). In contrast, pleasure ratings were tracked by activity in left inferior frontal gyrus and bilateral insula, which has been previously associated with processing positive emotions. These findings provide preliminary evidence for distinct appetitive components of nociceptive pain and may help elucidate why people intentionally engage in self-harming behaviors.

Disclosures: V. Rimeikyte: None. **J.L. Whitlock:** None. **A.K. Anderson:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.16/OO25

Topic: G.03. Emotion

Title: Relationship between growth mindset and stress

Authors: *C. FOX[1], I. DESTA[1], L. YOON[2], B. SHIBLEY[1], K. MOORE[1], S. PAJOR[1], M. DEANDA[1]
[1]Psychology, Holy Cross Col., Notre Dame, IN; [2]Psychology, Univ. of Notre Dame, Notre Dame, IN

Abstract: Research on Carol Dweck's Implicit Theory of Intelligence is relatively new. Studies have shown various beneficial effects of having or developing a Growth Mindset that reflects a belief that intelligence and abilities are plastic and subject to growth. However, very little research has been done on the relationship between Mindset and stress or anxiety. A preliminary study with 103 college students examined the effect of Mindset on five indicators of stress (physical, sleep, behavioral, emotional and personal habits) as well as anxiety and found that behavior stress is higher in subjects with Growth Mindset. More data is being collected and analyzed. Furthermore, we want to validate these results by collecting saliva cortisol measurements from subjects at the time of stress and anxiety testing. We plan to have the cortisol results ready for the Society for Neuroscience conference in November 2017. In conclusion, Growth Mindset might be beneficial for people but maybe at a cost of higher behavior stress.

Disclosures: C. Fox: None. **I. Desta:** None. **L. Yoon:** None. **B. Shibley:** None. **K. Moore:** None. **S. Pajor:** None. **M. DeAnda:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.17/OO26

Topic: G.03. Emotion

Title: Caffeine administration and elevated plus-maze exposure in rats activate populations of serotonergic neurons in the dorsal raphe nucleus relaxin-3 neurons in the nucleus incertus: Implications for the role of relaxin-3 in modulating serotonergic systems in the control of anxiety states

Authors: A. J. LAWTHER[1], *S. KENT[1], A. M. FLAVELL[1], S. MA[2], C. A. LOWRY[3], A. L. GUNDLACH[2], M. W. HALE[1]
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Abstract: Anxiety is a complex and adaptive emotional state controlled by a distributed and interconnected network of brain regions, and disruption of these networks is thought to give rise to the behavioural symptoms associated with anxiety disorders in humans. The dorsal raphe nucleus (DR), which contains the majority of forebrain-projecting serotonergic neurons, is implicated in the control of anxiety states and anxiety-related behaviour via neuromodulatory effects on these networks. However, the diverse functions of the serotonergic system means that drugs, such as SSRI's, which are used in the treatment of anxiety are often accompanied by unpleasant side effects, or are ineffective. Therefore, understanding how subsets of the serotonin system are modulated by other neurotransmitters, such as relaxin-3, may help improve our understanding of anxiety disorders, and lead to more targeted and effective treatments for these disorders. Relaxin-3 is the native neuropeptide ligand for the Gi/o-protein-coupled receptor, RXFP3, and is primarily expressed in the nucleus incertus (NI), a tegmental region immediately caudal to the DR. RXFP3 activation has been shown to modulate anxiety-related behaviour in rodents, and RXFP3 mRNA is expressed in the DR. In this study, we examined the response of anxiety-related brain regions, including relaxin-3-containing neurons in the NI and serotonergic neurons in the DR, following pharmacologically-induced anxiety and exposure to an aversive environment. We administered an anxiogenic dose of the adenosine receptor antagonist, caffeine (50mg/kg), or vehicle to adult male Wistar rats and, 30 min later, exposed them to either the elevated plus-maze or home cage control conditions. Immunohistochemical detection of c-Fos was used to measure activation of nuclei within anxiety related brain regions of the cortex, septum, amygdala, thalamus, hypothalamus and hippocampus, and to determine activation of serotonergic neurons in the DR and relaxin-3 neurons in the NI, measured 2 h following drug injection. Analysis revealed that caffeine administration and exposure to the elevated plus-maze

are both associated with an increase in c-Fos expression in relaxin-3-containing neurons in the NI, serotonergic neurons in the DR, and that these changes are associated with changes in c-Fos expression in multiple anxiety-related forebrain regions. These data are consistent with the hypothesis that relaxin-3 systems in the NI and serotonin systems in the DR interact to form part of a network involved in the control of anxiety-related behaviour.

Disclosures: A.J. Lawther: None. **A.M. Flavell:** None. **S. Ma:** None. **C.A. Lowry:** None. **A.L. Gundlach:** None. **M.W. Hale:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.18/OO27

Topic: G.03. Emotion

Support: CIC/COORDINATION OF SCIENTIFIC RESEARCH

Title: Anxiety: Ethanol and hydroxyzine oral consumption after reward devaluation

Authors: *L. MANZO[1], *L. MANZO[1], A. GORDILLO[2], A. C. TAFOLLA[2]
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Abstract: Male rats from the Low-avoidance strain (but not from the Roman High-avoidence strain) increased preference for ethanol after exposure to Appetitive extinction (Manzo et al. Physiol Behav 2014 123:86-92). Such increased fluid preference did not occur after acquisition (reinforced) sessions or in groups with postsession access to water, rather than ethanol. Because ethanol has anxiolytic properties in reward loss tasks, oral consumption after extinction sessions was interpreted as anti-anxiety self-medication. To test this hypothesis, Wistar (nonselected) rats received training in an instrumental extinction (reward loss) task in a straight alley after acquisition with continuous reinforcement (CR; 12 pellets per trial) vs. 50% partial reinforcement (PR; 12 or zero pellets per trial in random sequence) event in a PR situation were given a two-bottle, 2-h preference test immediately after extinction sessions. One of the two bottles contained 2% ethanol, 1 mg/kg hydroxyzine, or water for different groups (the second bottle contained water for all groups). Hydroxyzine is a anxiolytic used in the psychiatric treatment of individuals suffering from anxiety disorders. Three additional groups received the same postsession preference tests, but were always exposed to 12 pellets during CR. Rats showed during extinction session effect, suppressing behavior after the downshift relative unshifted controls. This effect was accompanied by a selective increase in both ethanol and hydroxyzine oral intake during the initial downshift sessions. Downshifted animals with access to water or unshifted controls with access to the anxiolytics failed to exhibit any changes in

preference during the postsession test. Such ethanol and hydroxyzine consumption depended on the degree of emotional activation induced by prior experience (i.e. PR vs. CR training) and also self-medication may provide insights into the early stages of addictive behavior.

Disclosures: L. Manzo: None. **A. Gordillo:** None. **A.C. Tafolla:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.19/OO28

Topic: G.03. Emotion

Support: UNAM DGAPA PAPIIT IN 204314

UNAM DGAPA PAPIIT IN 205217

CONACYT 22173

Title: Anxyolitic effects of oxytocin in nucleus accumbens

Authors: *S. D. GONZALEZ-GARCIA[1], A. D. HERNANDEZ[2], S. P. CAÑARTE-VARELA[2], E. N. LEVARIO-RAMIREZ[2], M. CRESPO[2], M. PEREZ DE LA MORA[2]
[1]UNAM Facultad de Medicina, Ciudad De Mexico, Mexico; [2]Neurociencia Cognitiva, UNAM Inst. de Fisiologia Celular, CDMX, Mexico

Abstract: Anxiety is an adaptative response which detects and protects an individual against danger. Nucleus accumbens is a brain structure that participates in modulation of emotion and motor behaviors. Several neurotransmitter and neuromodulators are involved in anxiety such as oxytocin that is a hypothalamic neuropeptide with anxiolitic effects into the brain. The paraventricular nucleus of hypothalamus projects oxytocinergic fibers to nucleus accumbens. However is less known about the role of oxytocin in the nucleus accumbens. The aim of this work was to evaluate the role of oxytocin in the nucleus accumbens in locomotions and anxiety behaviors. Here we used adult male wistar rats with weighting 240-260 g. Placed in a home cage Cycle dark light 12/12 (turn off lights 7:00). Oxytocin doses 0.3, 3 and 30 nanograms were injected intra accumbens. We used the open field test (50cm x 50 cm) to assess locomotor activity and anxiety behavior. In conclusion these results suggest that the oxytocin has no effect in locomotion activity in any doses used. In other hand the oxytocin at highest dose evoked an anxiolitic effect.

Disclosures: S.D. Gonzalez-Garcia: None. **A.D. Hernandez:** None. **S.P. Cañarte-Varela:** None. **E.N. Levario-Ramirez:** None. **M. Crespo:** None. **M. Perez de la mora:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.20/OO29

Topic: G.03. Emotion

Support: NIH Grant ZIAMH002798

Title: Induced anxiety impairs cognitive emotion regulation

Authors: *I. SARIGIANNIDIS[1,2], O. J. ROBINSON[1], J. ROISER[1], M. ERNST[2], C. GRILLON[2]
[1]Inst. of Cognitive Neurosci., London, United Kingdom; [2]NIMH-NIH, Bethesda, MD

Abstract: Cognitive conceptualisations of anxiety posit a central role of emotion regulation in the etiology of the disorder. In order to better understand the relationship between anxiety and emotion regulation, it is essential to disentangle the role of trait and state anxiety. Previous studies suggested that state anxiety dramatically impairs cognitive processes such as working memory and attention, processes that are essential for emotion regulation. Taking this into account, we investigated the possibility that state anxiety impairs an adaptive cognitive regulation strategy, reappraisal, whose underlying principles form the basis of cognitive behavioural therapy. We hypothesised that state anxiety will impair the ability to use reappraisal in order to modulate emotional responses. To this end, we used a well-validated technique, threat of unpredictable shock, to induce anxiety in healthy individuals while they performed an emotion regulation task. Participants viewed pictures and were asked to respond naturally, increase (upregulate) or decrease (downregulate) their negative response by reappraising the content of the pictures. Simultaneously, we recorded the magnitude of startle reflex, a widely used marker of emotional reactivity. Preliminary findings suggest that the difference in startle magnitude between conditions of upregulation and downregulation is diminished in the induced-anxiety condition. In other words state anxiety impaired to ability to use reappraisal to modulate emotional responses, in line with our hypothesis. Future studies could explore how the interaction between high trait and state anxiety affects the ability to regulate emotions, in order to better understand the role of emotion regulation in the pathogenesis of anxiety disorders.

Disclosures: I. Sarigiannidis: None. **O.J. Robinson:** None. **J. Roiser:** None. **M. Ernst:** None. **C. Grillon:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.21/OO30

Topic: F.02. Behavioral Neuroendocrinology

Support: University of Saint Joseph, Teaching and Learning Center

Title: Serotonin transporter inhibition induced behavioral alterations in *Drosophila*

Authors: *P. G. MANDELA
Dept. of Pharmaceut. Sci., Univ. of St. Joseph, Hartford, CT

Abstract: Our research goal is to identify the behavioral deficits that arise as a result of inhibiting serotonin transporter in *Drosophila melanogaster*. Drosophila serotonin transporter (dSERT) shares structural and functional similarities with human serotonin transporter (hSERT). Our preliminary results indicate that fluoxetine an SSRI, decreases locomotor activity in DAM and reiterative negative geotaxis (RING) experiments. These observations were in agreement with findings in rodent models. Most antidepressants alleviate despair behavior in rodent models. Drosophila demonstrates despair behavior when subjected to prolonged inescapable exposure to hot temperatures (37^{o}C). Our results demonstrate that pretreatment with fluoxetine drastically alleviated Drosophila despair behavior which was identical to observations in rodent behavioral models. These preliminary data supports our hypothesis that Drosophila serotonin transporter inhibition can produce behavioral effects similar to hSERT inhibition.In our future studies, we plan to establish other behavioral tests that can confirm antidepressant efficacy. We want to generate a Drosophila mutant that expresses GFP tagged hSERT which would enable us to overcome pharmacological differences at the same time monitor the transporter regulation. We also plan to create a complete SERT knockout Drosophila which enables us to delineate SERT dependent and independent effects of antidepressant drugs.

Disclosures: P.G. Mandela: None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.22/OO31

Topic: F.02. Behavioral Neuroendocrinology

Support: P30ES005022

Title: The effects of maternal exposure to organophosphate flame-retardants on offspring feeding and exploratory behaviors

Authors: *S. WALLEY[1], A. YASREBI[2], T. A. ROEPKE[3]
[1]Dept. of Animal Sci., Rutgers, New Brunswick, NJ; [2]Animal Sciences, SEBS, [3]Animal Sci., Rutgers, The State Univ. of New Jersey, New Brunswick, NJ

Abstract: Metabolic syndrome, while multifactorial, can be caused by endocrine disrupting compounds (EDC). Most EDCs are ubiquitous in the environment and accumulate in human tissues leading to concerns for potential effects during sensitive periods such as gestation and lactation. Organophosphate flame retardants (OPFR) are within one such group of EDCs that are found in many household products (furniture, toys, clothing electronics), with little data existing of OPFR effects on the fetus or neonate. OPFRs have agonistic/antagonistic activity for estrogen receptor alpha (ERα) and peroxisome proliferator-activated receptor (PPAR)γ, both are central pathways responsible for energy balance, motivated behaviors, and glucose homeostasis in the hypothalamus. We hypothesize that perinatal OPFR exposure impacts ERα-regulated genes in the hypothalamus leading to disruption of the hypothalamic melanocortin circuitry and alteration of activity in a sex-dependent manner. To test our hypothesis, we fed antenatal WT mice a peanut butter and OPFR mixture (triphenyl phosphate, tricresyl phosphate, and tris(1,3-dichloro-2-propyl) phosphate) from GD7 to PND14 and measured anxiety like behaviors (EPM and OFT) on week 19. Subsequent experiments will characterize the impact of OPFRs on metabolic parameters.

Disclosures: S. Walley: None. **A. Yasrebi:** None. **T.A. Roepke:** None.

Poster

698. Emotional States: Anxiety and Pain

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 698.23/OO32

Topic: F.02. Behavioral Neuroendocrinology

Title: The role of ERa-mediated ERE-dependent and ERE-independent signaling in feeding and exploratory behaviors in male and female mice

Authors: *A. YASREBI[1,3], T. A. ROEPKE[2]
[1]Animal Sciences, SEBS, [2]Animal Sci., Rutgers, The State Univ. of New Jersey, New Brunswick, NJ; [3]Grad. Program in Endocrinol. and Animal Biosci., Rutgers Univ., New Brunswick, NJ

Abstract: The reproductive steroid hormone, 17β-estradiol (E2), control feeding and exploratory behaviors associated with mood disorders. The loss of circulating E2 puts menopausal woman at a increased risk for developing obesity and mood disorders when compared to premenopausal woman. Therefore, it is critically important to understand the role of sex steroids and their receptors in the neuroendocrine control of feeding and mood. The goal of this project is to understand the role of estrogen response Element (ERE)-dependent and ERE-independent ERα signaling on behavior by characterizing feeding patters and exploratory behaviors in male and female mice lacking either total ERα signaling or lacking ERE-dependent ERα signaling. We hypothesize that ERE-independent ERα is partially sufficient to restore feeding and exploratory behaviors that are lost in total ERα knockout mice. We tested three strains of mice: two ERα transgenic models, a total ERα knock out (ERKO) and a novel ERα knock in/knock out (KIKO) that lacks a functional DNA-binding domain) and their wild type (WT) C57 littermates using a real-time feeding behavior monitoring system and series of standard behavior tests (open field tests, elevated plus maze, forced swim test). Each experiment was initially done with intact animals and then again repeated in ovariectomized (OVX) animals split into either an oil treated control group or an E2-treated group. By using these ERα transgenic mouse models, we will investigate the contribution of ERE-mediated ERα signaling in controlling feeding and exploratory behaviors.

Disclosures: A. Yasrebi: None. **T.A. Roepke:** None.

Poster

699. Emotional States

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 699.01/OO33

Topic: G.03. Emotion

Support: JSPS 15K12069

Title: What is happening in our brain when we feel music-induced chills and don’t feel chills?

Authors: *A. YANG, K. I. KOBAYASHI
Doshisha Univ., Kyoto, Japan

Abstract: We sometimes feel extremely pleasant when we listen to music. This emotion is called chills. The sensation of chills is so strong that it is far beyond the ordinary sense of pleasure frequently resulting in goose bumps or shivers. The purpose of this study is to find out the neural mechanism of musical chills sensations. We investigated the difference in brain activities when a “chill” sensation occurs and when it doesn’t while listening to an identical music by using fMRI. We aimed to identify the specific activation related to the chills. Thirteen subjects listened to four pieces of music. These pieces were selected by each subject and

expected to cause the sensations. We defined them as original music. To prevent the subjects from feeling the sensation, we added noise to four pieces of music (noisy music). In total, subjects listened to eight stimuli (four pieces of original music and four pieces of noisy music) under the MRI scan. In the experiment, they reported whether they were feeling chills or not by pressing a button. We defined feeling chills as chill-on and defined not felling chills as chill-off. We measured and compared the brain activity of each subject. In the results, noisy music significantly shortened the average duration of chills compared with original music. As for fMRI analysis, brain activities during chill-on condition caused by original music contrasted with during chill-off condition caused by original music showed significant increase of activities in the caudate. The same region was activated when subjects felt chills in noisy music condition. It suggests that the caudate is the key to distinguish the difference of chill-on and chill-off. Next, brain activities during chill-on condition caused by original music contrasted with during chill-on condition caused by noisy music showed significant increase of activities in the putamen, the insula and the parahippocampus. The same regions were activated during chill-off condition caused by original music contrasted with during chill-off condition caused by noisy music. It suggests that the activation areas are not exclusively related to the chills, rather helped to feel chill when subjects listened to chill-inducing music. Based on our research, the activation in the caudate could be important for the chill sensation. In addition, the activation in the putamen, the insula and the parahippocampus could be involved in general musical sensation, such as whether they listened to original or noisy music. Our research will contribute to find out the neural mechanism of chills.

Disclosures: **A. Yang:** None. **K.I. Kobayashi:** None.

Poster

699. Emotional States

Location: Halls A-C

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Program#/Poster#: 699.02/OO34

Topic: G.03. Emotion

Title: Stress Reduction from a Music Intervention

Authors: *E. E. LEAVER[1], L. ST. PIERRE[1], R. WARFIELD[1], B. HEARN[1], H. ENNERFELT[2], V. FALLON[1]
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Abstract: Research suggests that music listening can affect mood (McGregor et al. 2011) and physiological states (Thoma et al. 2013). Much of this research has focused on long-term effects occurring over the course of multiple sessions and many of the studies have focused on behavioral variables such as self-reported changes in mood that result from music intervention. The purpose of this Stress Reduction with a Musical Intervention study was to expand the

previous work in two major ways. We wanted to compare the stress reducing effects of music listening versus music playing. Secondly, we utilized psychophysiological measures of stress in addition to self-report measures. We were also interested in changes that occur in one session (as opposed to multiple sessions). Specifically, participants were exposed to a stressor task while recording EDA measures. Self-report behavioral measures were also assessed. After the stressor task was complete, participants were assigned to one of three recovery conditions; Control (CG), Music Listening (ML), or Music Playing (MP). Behavioral and physiological results from post stressor and post recovery were compared. We performed a manipulation check by comparing baseline behavioral and physiological data versus post stressor data for each subject to ensure that we successfully stressed the participants. Results indicated that participants exhibited significant increase in behavioral and physiological stress response as a result of the stressor task. In comparing the groups, behavioral data was mixed while the physiological data showed a trend towards greater stress reduction for both experimental groups.

Disclosures: E.E. Leaver: None. **L. St. Pierre:** None. **R. Warfield:** None. **B. Hearn:** None. **H. Ennerfelt:** None. **V. Fallon:** None.

Poster

699. Emotional States

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 699.03/DP11/OO35 (Dynamic Poster)

Topic: G.03. Emotion

Support: Faculty Research Council Grant

Title: Measuring physiological markers of restorative landscapes using virtual reality environments

Authors: *M. MURARIK[1], *C. L. JIMENEZ CHAVEZ[2], J. LADNER[2], T. PEGORS[2]
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Abstract: Nature is often referred to by many as the fountain of inspiration, peace, and restoration. Research has shown that even minimal exposure to natural environments has been associated with increases in cognitive performance, attention and mood. Additionally, studies have shown significant decreases in stress after such exposure. What remains unknown, however, are the physiological responses during nature exposure and their relationship to these post-exposure changes in stress and behavior. In this study, we used ECG to measure heart rate variability (HRV) while participants were exposed to two nature and two urban environments in a virtual reality (VR) paradigm. Using VR rather than real-world exposure allowed us to move the subject through immersive environments without inducing physical exertion on the participant's behalf. Each subject was exposed to four environments (design using Unity

software): an open valley, a narrow forest, an open plaza, and a narrow street. Environment order was counterbalanced between participants. Within each environment, participants were transported to six locations for 30s within the environment. Participants were asked to remain seated and refrain from excessive movement below the neckline, but they were encouraged to look around within their environment and to take pictures of beautiful views. (An Oculus Rift VR unit was used to provide a 360 degree, high-resolution spatial view.) An initial 6m baseline HRV was collected after a practice environment, then 3m resting baselines were introduced before each environment. After 30-min VR exposure, participants exited VR and were then asked to create a brochure of their top-ten views (created with custom code), describing and ranking the pictures they themselves had taken. Using time domain measures, the standard deviation of the normal-to-normal intervals (SDNN) was lower for urban environment immersion than for natural environment immersion. Additionally, root mean square of the successive difference values (RMSSD) was higher for natural environments than for urban environments, thus indicating higher parasympathetic activity during nature immersion. Additional analyses will correlate differences in HRV to behavior measures, including 1) number of pictures taken, 2) ranking of pictures, 3) verbal description of pictures. Given that people tend to have some control over their environment, pinpointing the physiological mechanisms underlying the benefits of natural environments is important to making changes that increase our health, cognitive abilities, and psychological well-being.

Disclosures: M. Murarik: None. **C.L. Jimenez Chavez:** None. **J. Ladner:** None. **T. Pegors:** None.

Poster

699. Emotional States

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Topic: G.03. Emotion

Support: NSFC31470997

NSFC81171289

Title: Focusing on slow breathing modulates early and late components of affective pictures

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Abstract: An emerging body of research has applied breath-focused attention training in mindfulness interventions to reduce multiple symptoms of stress, anxiety, and depression. However, yet little is known regarding the neural mechanism of how focusing on slow breathing modulates time course of emotional responses. Here we recorded event-related potentials (ERPs) of 20 healthy undergraduate volunteers when they performed a breath-focused attention task during the viewing of affective pictures. Before the experiment, all the participants were instructed to practice slow breathing for 3 minutes. In the viewing condition, early component (P1, N1, and N2) and late positive potential (LPP) amplitudes to affective pictures increased more than those to neutral pictures. However, focusing on the sensation of slow breathing attenuated affective modulation of these ERPs. In the breath-focused condition but not in the viewing condition, P1 amplitudes for emotional minus neutral pictures correlated positively with the ability to focus attention measured by the Attentional Control Scale; N2 amplitudes for emotional minus neutral pictures correlated positively with individual differences in dispositional mindfulness measured by the Mindful Attention Awareness Scale. However, LPP amplitudes for emotional minus neutral pictures predicted subsequent arousal rating scores for emotional minus neutral pictures, regardless of the viewing or breath-focused condition. These observations suggest that even in the face of emotional stimulation, focusing on slow breathing induces attention-concentrated mindful states that increase the stability of attention and promote early emotion regulation, which deepens our understanding of the temporal processing mechanism of breath-focused mindfulness.

Disclosures: W. Zhang: None. **L. Liang:** None. **P. Li:** None. **X. Liu:** None. **B. Sun:** None. **H. Li:** None.

Poster

699. Emotional States

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Program#/Poster#: 699.05/PP1

Topic: G.03. Emotion

Support: Swedish Research Council grant 2011-1529

Marcus och Amalia Wallenbergs Minnesfond IC (MAW 2014.0009)

Title: Neural and autonomic responses to long-lasting slow stroking

Authors: *C. TRISCOLI[1], G. HÄGGBLAD[2], P. HAMILTON[3], S. STEUDTE-SCHMIEDGEN[4], H. OLAUSSON[6], I. CROY[5], U. SAILER[7]
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Sweden; [4]Dept. of Psychology, [5]Clin. for Psychosomatic Med., Technische Univ. Dresden, Dresden, Germany; [6]Ctr. for Social and Affective Neuroscience, Dept. of Clin. and Exptl. Med., Linkoping Univ., Linkoping, Sweden; [7]Fac. of Medicine, Inst. of Basic Med. Sciences, Dept. of Behavioural Sci. in Med., Oslo Univ., Oslo, Norway

Abstract: Introduction: Ongoing slow stroking is perceived as pleasant over an unexpectedly long time (Triscoli et al., 2014). Low threshold, unmyelinated C-tactile afferents respond preferentially to this type of touch. In two studies, we investigated both neural and autonomic (heart rate variability) responses during long-lasting slow stroking.
Methods: In both studies, stroking was performed with a brush on the forearm for ~ 40 minutes at 3 cm/s (the velocity that optimally activates C-tactile fibres). In study 2, we added a control group (20 subjects) that received vibration stimulation. In study 1, 25 subjects were scanned with functional magnetic resonance imaging. In study 2, we calculated heart rate variability (HRV) in 40 subjects. In both studies, pleasantness ratings for the brush stroking (and vibration in study 2) were collected.
Results: In both studies, stroking was never rated as unpleasant; the perceived pleasantness of stroking, however, declined over time. In study 1, activation in primary and secondary somatosensory cortices (S1 and S2) decreased over time while activation in orbito-frontal gyrus (OFC) and putamen strongly increased until plateauing after 20 min. Only at the end of the stimulation, posterior insula, middle cingulate and striatal regions became functionally connected. In study 2, HRV increased during brush stroking, but not vibration. Interestingly, both OFC activation and HRV increased up to 20 minutes from the onset of brush stroking and plateaued afterwards.
Discussion: Similar increases in OFC activation and HRV over a common interval suggest a link between neural and autonomic systems in response to long-lasting stroking performed at C-tactile optimal velocity. OFC activation may reflect updating of reward value. Increased HRV found for stroking, but not for vibration, may reflect adaptive self-regulation to emotional stimuli. Our findings highlight parallel time courses for the neural and autonomic adaptation to pleasant tactile experiences.

Disclosures: C. Triscoli: None. **G. Häggblad:** None. **P. Hamilton:** None. **S. Steudte-Schmiedgen:** None. **H. Olausson:** None. **I. Croy:** None. **U. Sailer:** None.

Poster

699. Emotional States

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Topic: G.03. Emotion

Support: John D. and Catherine T. MacArthur Foundation or the MacArthur Foundation Research Network on Law and Neuroscience

Title: The Fusiform Face Area shows distinct patterns of fMRI activity to African American and Caucasian faces in different emotional contexts

Authors: *B. NARDOS[1], E. RUBIEN-THOMAS[3], E. E. SCHIFSKY[2], B. J. CASEY[4], D. A. FAIR[5]
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Abstract: Recent events in the United States have brought to the forefront issues related to the presence and severity of racial discrimination towards African Americans. While emotions often run high in these discussions, empirical evidence describing differential brain responses in individuals confronted with African American (AF) versus Caucasian (CAU) faces is lacking. In addition, how these brain responses might differ in emotionally arousing contexts is also unclear. Using an emotional go/no-go impulse control fMRI task in two independent groups of healthy AF and CAU young adults (Dataset 1: AF - N=17, mean age 23, 5 female; and CAU - N=39, mean age 21, 23 female; Dataset 2: AF - N=44, mean age 26, 22 female; and CAU - N=39, mean age 27, 21 female), this study explored potential differences in brain activity related to processing black versus white faces with different emotional expressions (calm, happy, fearful) in different sustained emotional contexts (neutral, negative, positive). The fusiform face area (FFA), a brain region involved in processing face stimuli, emerged as one of the brain regions whose activity was sensitive to the interactive contributions race and emotional context. Black and white faces elicited similar levels of activity in FFA in neutral contexts, while exhibiting differential levels in emotional contexts. In positive contexts greater activity was elicited for Caucasian faces; whereas in negative contexts greater activity was elicited for African American faces. fMRI activity in the noted brain regions was correlated with the level of false alarms in the GO/NO-GO task as well as Implicit Association Test scores, with different patterns of brain/behavior relationships as a function of race and emotional context. Participant race had no bearing on these findings. These results indicate inherent differences in how the brain responds to race in a context-dependent manner.

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Poster

699. Emotional States

Location: Halls A-C

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Program#/Poster#: 699.07/PP3

Topic: G.03. Emotion

Support: Ke: NIH R01MH097320

Title: Multivoxel pattern analysis of affective picture processing: A simultaneous EEG-fMRI study

Authors: *K. BO[1], S. YIN[2], Y. LIU[3], A. KEIL[4], M. DING[5]
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Abstract: Both electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) studies have shown that affective pictures elicit enhanced visual processing relative to neutral pictures. The latency of this enhanced visual processing, as indexed by the EEG late positive potential (LPP), is consistent with the reentry hypothesis. In this study, recognizing that univariate analysis employed up to date has limited capability in uncovering distributed neural representations, we examined the multivoxel patterns evoked by affective pictures. Simultaneous EEG-fMRI were recorded from healthy subjects during passive viewing of pleasant (erotica, romantic courtship, sport scenes), neutral/calm (house hold scenes, people), and unpleasant (mutilation, human violence, attacking animals) pictures, selected from the International Affective Picture System (IAPS). Each picture was shown for 1000ms. The inter-trial interval (ITI) varied randomly from 6000 to 9000ms. Applying the support vector machine (SVM) technique to single-trial BOLD responses obtained using the beta-series method, we decoded pleasant-versus-neutral conditions and unpleasant-versus-neutral conditions. The following results were found. First, the decoding accuracy is above chance level in all areas along the visual hierarchy. Second, the decoding accuracy follows a top-down cascading pattern, with high-order visual areas having higher decoding accuracy than low-order visual areas. Third, the decoding accuracy is positively correlated with the magnitude of LPP, a well-established index of motivationally facilitated attention. Collectively, these results show that emotionally arousing stimuli are distinctively represented in the visual system, and that enhanced visual processing of these stimuli is effected by re-entrant projections originating in high-order emotional processing areas of the brain.
Keywords: emotion; fMRI; multivariate pattern analysis; late positive potential; re-entrant projection

Disclosures: K. Bo: None. **S. Yin:** None. **Y. Liu:** None. **A. Keil:** None. **M. Ding:** None.

Poster

699. Emotional States

Location: Halls A-C

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Program#/Poster#: 699.08/PP4

Topic: G.03. Emotion

Support: Equipment provided by SPARK Neuro

Title: Investigation of Emotional Valence using EEG

Authors: *W. R. MCGARRY
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Abstract: Neural activity reflecting emotional valence has been a large topic of study for decades, yet there is still a great deal of conflict in the literature pertaining to which neural features are thought to reflect positive and negative emotional valence. The purpose of this study was to investigate the specific neural signals believed to reflect emotional valence. EEG recordings were obtained as participants were given a visual emotion processing task. Results demonstrated empirical support for specific neural features underlying positive and negative states of emotional valence.

Disclosures: W.R. McGarry: A. Employment/Salary (full or part-time):; SPARK Neuro full-time. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Equipment from SPARK Neuro.

Poster

699. Emotional States

Location: Halls A-C

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Topic: G.03. Emotion

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Title: Temporal and spectral changes of human EEG according to emotional arousal

Authors: *H. KIM, ***H. KIM**, P. SEO, D. YEO, S. HER, J. CHOI, J. CHOI, K. KIM
Bio medical engineering, Yonsei Univ., Wonju, Korea, Republic of

Abstract: Background: An emotional arousal refers to perceived activation state to the proprioceptive feeling of physiological arousal induced by an affective stimulus. Neural mechanisms underlying the emotional states are not identified. Here we tried to investigate the changes in cortical activities according to emotional arousal states during watching emotional

video clips. **Methods**: Twenty healthy university students participated in the experiment. Thirty-two affective video clips were presented in one-minute. Sixty-four channel electroencephalograms (EEGs) were recorded. The alpha and gamma frequency bands within 30 - 50 seconds intervals were selected as the region of interest by applying a mass univariate analysis (MUA). Subsequently, statistical comparison between high and low arousal was performed using two sample t-test. False discovery rate correction (FDR<0.05) was used for multiple comparison. **Results**: The power within the time-frequency window of interest (alpha and gamma bands, 30 - 50 seconds) was significantly different between high and low arousals. Widespread alpha power was significantly decreased in high arousal (FDR<0.05). Strong alpha activity was observed at frontal and left parietal areas (FDR<0.01). In contrast, gamma powers in lateral temporal and parietal areas were significantly increased for high arousal. Furthermore, the alpha powers were found to be significantly anti-correlated with self-assessment scores of arousal. **Conclusion**: The widespread alpha and temporoparietal gamma bands powers were highly correlated with arousal. In line with previous studies, the widespread suppression of alpha power in high arousal may represent cortical disinhibition by affective attention. These characteristic changes in EEG would provide useful biomarkers for the design of pattern classifiers for emotion recognition.

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Poster

699. Emotional States

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Title: Time-frequency analysis of the electroencephalogram evoked by skin conductance response to emotional events

Authors: P. SEO, H. KIM, D. YEO, S. HER, J. CHOI, J. CHOI, *K. KIM
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Abstract: Emotional status affects the physiological signals reflecting the activities of central and autonomic nervous systems (CNS and ANS). However, the relationship between the physiological signals of the CNS and ANS was not investigated. Here we tried to identify the relationship between two major arousal indicators, electroencephalogram (EEG) and skin conductance response (SCR) evoked by emotional events. Seventeen healthy university students participated in the experiment. Multichannel EEGs and electrodermal activity (EDA) were recorded during watching movie clips extracted from Korean movies, intended to evoke emotional arousals. The SCR peaks were detected from the EDA signal, and the SCR peaks larger than 10% of the maximum SCR peak amplitude were further analyzed. The EEG segments within -3500~3500 ms epoch around the SCR peaks were obtained. Time-frequency analysis was performed to obtain event-related spectral perturbation (ERSP). To investigate characteristic changes in the SCR-related EEGs, the statistical comparison of the ERSPs were made between the ERSPs of SCR-related EEGs and baseline EEGs without SCR responses. Significant differences were found mostly in bilateral central areas. Alpha- and beta-band powers were significantly increased for the SCR-related EEGs, mainly during -2500~2500 ms, compared to baseline conditions. Right centrotemporal region showed increased alpha-band power, and left centrotemporal region showed increased beta-band power. This increases could be related with asymmetric activities due to the emotionally arousing events in the movie stimuli.

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Poster

699. Emotional States

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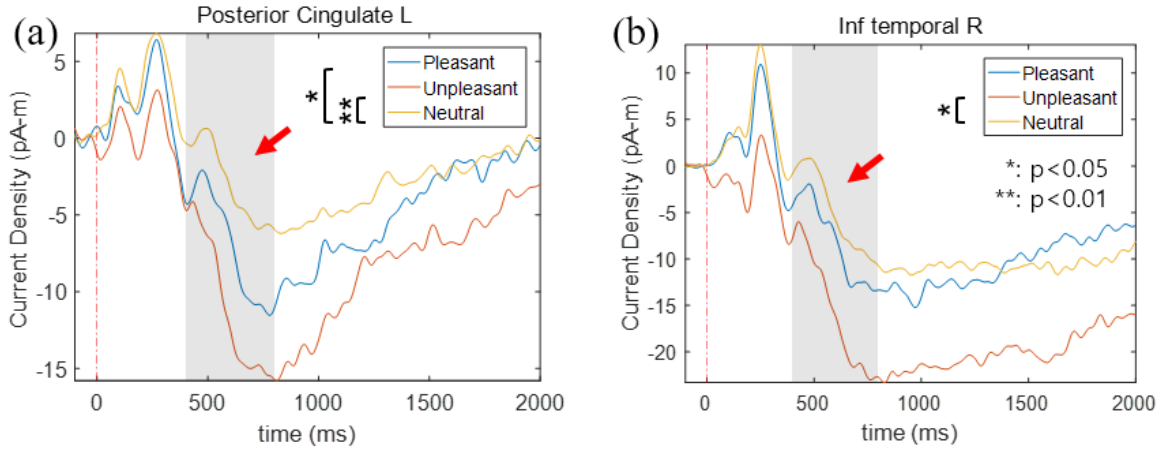
Support: This research was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Korea government (MSIP) (No.2015R1D1A1A01056743)

Title: Changes in posterior cingulate cortex current density in response to emotional visual stimuli

Authors: *D. YEO, J. CHOI, K. CHA, H. KIM, P. SEO, S. HER, K. KIM
Yonsei Univ., Wonju / Gangwon-Do, Korea, Republic of

Abstract: In this study, we investigated event-related changes of cortical current density in response to emotional visual stimuli. Nineteen healthy male subjects without neurological and psychiatric illness were enrolled in the experiment (age: 23.18±1.92 years). 64-channel

electroencephalogram (EEG) was recorded while the subjects were watching pleasant, unpleasant and neutral pictures. Event-related potential (ERP) at scalp electrodes and event-related changes of cortical current source density were analyzed. For the event-related current density analysis, mass univariate analysis was applied after source localization with weighted minimum norm estimation. Significant increase of the cortical current density was found in right inferior temporal cortex (ITC) and left posterior cingulate cortex (PCC) in late temporal epoch (400-800 ms). The current density level was proportional to the arousal level. It is well known that ITC deals with color or shape of visual stimuli and relates to visual memory. It is recognized that PCC is related to retrieval of episodic memory. Recent studies suggest that PCC performs functions related to emotional evaluation as well. The most significant activation of PCC in our results may imply that the PCC plays more important role in evaluating emotion than previous assumptions.



Disclosures: **D. Yeo:** None. **J. Choi:** None. **K. Cha:** None. **H. Kim:** None. **P. Seo:** None. **S. Her:** None. **K. Kim:** None.

Poster

699. Emotional States

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Topic: G.03. Emotion

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Title: Dopamine D1 and D2/3 receptor antagonism effect on tickling induced 50-kHz ultrasonic vocalizations in the adolescent rats

Authors: *M. HORI[1], R. SHIMOJU[2], J. OHNISHI[4,1], K. MURAKAMI[1], M. KUROSAWA[2,3]
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Abstract: Adolescence, the transition period between childhood and adult life, is a critical period for neural and social development. The maturation of dopaminergic neurotransmitter systems, particularly in the prefrontal cortex and limbic regions, also occurs during adolescence, and determines the sensitivity to rewarding effects of food and drugs, etc.
Additionally, social interactions are important for neuronal and behavioral development. Therefore, social isolation is noxious and increase the stress vulnerability, whereas play behavior during juvenile and adolescence is considered to facilitate neural and social development in rodents. Since the level of rough-and-tumble play is regulated by pharmacological manipulations of brain dopamine system, rough-and-tumble play is thought be itself a kind of “pleasure or joy”. Meanwhile, adolescent rats emit 50-kHz ultrasonic vocalizations (USVs), a marker of positive emotion, during rough-and-tumble play. The emission of 50-kHz USVs is mediated by dopamine release in the nucleus accumbens. We recently showed that tickling, which mimic rough-and-tumble play with human hand, triggers dopamine release with 50k-Hz USVs in the nucleus accumbens, and tickling-induced 50-kHz USVs were inhibited by the direct microinjection of dopamine receptor antagonist into the nucleus accumbens.
In the present study, we investigate whether there are differences between D1 and D2/3 receptor subtypes antagonism to response by tickling in the nucleus accumbens. As a result, D1 or D2/3 receptor antagonism alone altered the production of 50kHz USVs, but also these dopamine receptor subtypes appear to influence acoustic parameters to different degrees. Pretreatment with raclopride, D2/3 receptor antagonist, inhibited the expression of positive emotion faster than that with SCH23390, D1 receptor antagonist, since the numbers of 50-kHz calls in the raclopride treatment group was lower than those in the SCH23390 treatment group at 2min after the antagonist administration. These results may indicate that during adolescence the potentially different contributions receptor subtypes play in positive emotion control in the nucleus accumbens.

Disclosures: M. Hori: None. **R. Shimoju:** None. **J. Ohnishi:** None. **K. Murakami:** None. **M. Kurosawa:** None.

Poster

699. Emotional States

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Topic: G.03. Emotion

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Title: HPA axis activation in various tasks evaluating memory and anxiety

Authors: *N. L. GARCIA SALDIVAR[1], M. R. A. GONZÁLEZ-LÓPEZ[2], S. E. CRUZ-MORALES[2]
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Abstract: Components of different behavioral procedures that evaluate memory and anxiety generally involve a training session and a test session. Each session may contain stressors that activate the adrenal hypothalamic-pituitary axis (HPA) differentially. Thus, in the task of inhibitory avoidance (IA), the stressor is the shock; in the Elevated T-Maze (ETM) and Elevated Plus-Maze (EPM) the open spaces are the stressors, while the task of object recognition (RO) seems to have no stressors. The objective of the present study was to evaluate the stressful effect of the components of various tasks used in the study of memory and anxiety. Eight groups of male rats (N = 8) were assigned to one of the following treatments: control (C), 2 groups exposed to IA, 2 groups exposed to ETM and two more groups exposed to OR, in all cases one group of each procedure was exposed to training session (T IA, T ETM, T OR) or to training and test sessions (IA, ETM, OR); one more group was exposed to the EPM. The subjects were sacrificed immediately after training and a blood sample was obtained to measure the concentration of corticosterone in plasma by ELISA. The release of corticosterone was greater in the subjects during the training phase in the RO task than in all groups, whereas when the two training and test sessions were performed in all the tasks, no significant differences were observed, although there is a tendency in the group exposed to IA training and testing to show a higher concentration of corticosterone. Although it has been proposed that the task of MRO is a less aversive task, the first session involves the participation of an event that activates the HPA axis and this factor has to be considered when evaluating the effect of other stressors on memory.

Disclosures: N.L. Garcia Saldivar: None. **M.R.A. González-López:** None. **S.E. Cruz-Morales:** None.

Poster

699. Emotional States

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Schapiro Undergraduate Research Fellowship, R-MC

Title: Neurobiological components of varying coping strategies: Influence of behavioral, endocrine, neural and dynamic genome markers

Authors: *K. G. LAMBERT[1], J. PERDOMO-TREJO[2], M. KENT[1], C. SYDNOR[1], A. A. BARTLETT[3], H. E. LAPP[3], S. SCAROLA[2], S. NEAL[2], B. THOMPSON[2], S. LAMBERT[2], D. VAVRA[1], M. BARDI[2], R. G. HUNTER[3]
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Abstract: Although Hans Selye described the *general* adaptation syndrome highlighting similar stress responses within and across species, subsequent research has identified individual differences associated with stress responsivity. Given the influence of certain patterns of stress responsiveness on the emergence of various illnesses, it is important to identify relevant neurobiological markers associated with susceptibility to maladaptive stress responses. In the current study, two cohorts of rats were investigated to examine neurobiological correlates of varying coping strategies. In the first study, male rats profiled as passive, active or flexible copers via the back-test restraint assessment adapted for rats in our laboratory (n=8 each group) were exposed to a problem-solving digging task and a novelty suppressed feeding task. Following the problem-solving challenge, fecal samples were collected and subsequent assays indicated that the flexible copers had higher DHEA levels (associated with emotional resilience) than active and passive copers ($p<.005$). In the feeding task, flexible profiled rats exhibited more exploratory behavior in the form of rearing responses, but consumed less food ($p=.03$ and .04, respectively). One hemisphere of each brain was subsequently processed for Golgi/Cresyl double staining; the other hemisphere was processed for BDNF-immunoreactivity (ir). Preliminary data indicate that the passive copers have less dense dendritic spines in the anterior cingulate cortex; BDNF-ir is currently being quantified. In a second cohort of 34 coping-profiled male and female rats (n=4-6 per group), a nonsignificant trend indicated that flexible copers exhibited a longer latency to cross a novel barrier to consume a food reward ($p=.08$). Hippocampus tissue was processed for markers of epigenetic regulation and, in the males, a marginally significant effect of coping strategies was observed for H3K9me3 levels ($p=.055$), with the largest difference between the passive and active animals. Further, a significant effect of coping profile on B2 SINE RNA, a retrotransposon implicated in stress induced regulation of global gene expression, was observed ($p=.001$), with flexible copers exhibiting higher levels than active copers. In sum, these findings suggest that individual mammalian responses to perceived threats are associated with the activation of a multifaceted cascade of neurobiological events. Further research is needed to illuminate the complex associations among these variables and relevant influence on adaptive stress responses.

Disclosures: **K.G. Lambert:** None. **J. Perdomo-Trejo:** None. **M. Kent:** None. **C. Sydnor:** None. **A.A. Bartlett:** None. **H.E. Lapp:** None. **S. Scarola:** None. **S. Neal:** None. **B. Thompson:** None. **S. Lambert:** None. **D. Vavra:** None. **M. Bardi:** None. **R.G. Hunter:** None.

Poster

699. Emotional States

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 699.15/PP11

Topic: G.03. Emotion

Support: NIMH Grant MH107742

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Searle scholar program

Klingenstein Foundation

Whitehall Foundation

Title: Discrete roles for the ventral pallidum in depression

Authors: *D. KNOWLAND, V. LILASCHAROEN, C. PACIA, S. SHIN, E. WANG, B. LIM
UCSD, San Diego, CA

Abstract: Patients with major depressive disorder (MDD) display a common, but often variable set of symptoms making successful, sustained treatment difficult to achieve. Separate depressive symptoms in patients may be encoded by differential changes in distinct neural circuits in the brain, yet how discrete circuits underlie behavioral subsets of depression and how these circuits adapt in response to stress has not yet been addressed. We have identified two discrete circuits of parvalbumin-positive (PV) neurons in the ventral pallidum (VP) projecting to either the lateral habenula (LHb) or ventral tegmental area (VTA) contributing to depression. First, we surprisingly find that a subpopulation of PV neurons are glutamatergic. Next, we observe that these populations undergo different electrophysiological adaptations in response to social defeat stress, which are normalized by antidepressant treatment. Furthermore, manipulation of each population separately mediates either social withdrawal or behavioral despair behaviors, but not both. These results propose that distinct components of the ventral pallidal parvalbumin-positive circuit can subserve related, yet separate depressive-like phenotypes in mice which could ultimately provide a platform for symptom-specific treatments of depression.

Disclosures: D. Knowland: None. **V. Lilascharoen:** None. **C. Pacia:** None. **S. Shin:** None. **E. Wang:** None. **B. Lim:** None.

Poster

699. Emotional States

Location: Halls A-C

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Program#/Poster#: 699.16/PP12

Topic: G.03. Emotion

Support: Intramural Research Program of the NIMH

Title: Inhibitory control of a thalamic stress circuit

Authors: B. S. BEAS[1], B. J. WRIGHT[1], Y. LENG[1], O. KOITA[1], N. RINGELBERG[1], *M. A. PENZO[2], *M. A. PENZO[1]
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Abstract: Stress typically leads to adaptive responses aimed at reinstating homeostasis. However, stress is also known to both exacerbate and facilitate the onset of several psychiatric conditions including anxiety and depressive disorder. Surprisingly, our knowledge of the neuronal circuits controlling the impact of stress on behavior is far from complete. The paraventricular nucleus of the thalamus (PVT), a member of the midline thalamic nuclei, has recently emerged as a candidate structure bridging the gap between stress sensing and stress responding. The PVT shares anatomical connections with several brain areas involved in stress processing, such as the amygdala, the nucleus accumbens, and the medial prefrontal cortex. In addition, PVT is activated following a wide range of physical and psychological stressors, and has been previously proposed to be the ‘stress memory’ center of the brain However, the neuronal mechanisms and afferent inputs to the PVT that enable its recruitment following a stress event remain unknown. Here we addressed this question using a combination of fiber photometry, optogenetics, and chemogenetics to investigate both the mechanisms and neuronal circuitry involved in the recruitment of PVT circuits by stress. Our results indicate that a long range input to the PVT triggers a rapid and persistent decrease in GABAergic inhibition that contributes to the formation of a stress memory and the control of stress susceptibility.

Disclosures: B.S. Beas: None. **B.J. Wright:** None. **Y. Leng:** None. **O. Koita:** None. **N. Ringelberg:** None. **M.A. Penzo:** None. **M.A. Penzo:** None.

Poster

699. Emotional States

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Topic: G.03. Emotion

Support: JSPS KAKENHI 15K18347

Shimazu Science Fundation

Narishige Neuroscience Research Fundation

Title: Dual processing in the primate dorsal raphe nucleus for choice behavior under different mood

Authors: *M. YASUDA, Y. UEDA, K. NAKAMURA
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Abstract: The emotion often affects decision making. It is thus important to understand emotions in terms of their effects on cognitive behavior. Previously, we found that many neurons in the dorsal raphe nucleus (DRN) were modulated by emotional contexts. The DRN neurons also exhibited activity associated with reward-seeking behavior. To investigate whether and how the emotional and cognitive processing are represented in single DRN neurons, we recorded neuronal activity in DRN while a monkey performed a reversal choice task, but manipulating its emotion by presenting conditioned cues.
In the task, after fixation on the central fixation point, two different objects were presented simultaneously in left and right. The monkey chose one of them by making a saccade. A reward was given for one object (correct) but not for the other (wrong trial). The object-reward contingency was fixed for a block of trials, but it was reversed after reaching a behavioral criterion. To manipulate the monkey's emotion, we chose one of three emotional cues, previously-learned reward (appetitive) -, tone (neutral) -, or air puff (aversive) -associated CS, and presented it in the inter-trial interval (ITI) during consecutive 2 blocks. We monitored the monkey's heart rate and pupil size as biological markers of emotional state.
We observed significantly larger pupil diameter and higher heart rate in aversive than in the other two emotional states, suggesting emotional stress. The 108 task-related DRN neurons were equally divided into three sub-populations depending on overall responses in each emotional state: ‘appetitive-highest’ (33%), ‘neutral-highest’ (33%), or ‘aversive-highest’ (33%). The neurons were also grouped in relation to monkey’s performance; “correct type” or “wrong type”. The ‘correct-type’ neurons were characterized by their sustained increase in activity during central fixation and the stronger activity in correct than wrong trials during ITI and/or fixation period, suggesting the contribution of preparatory signal for making correct choice. The wrong-

type neurons were characterized by sustained decrease in activity during central fixation and enhanced response after wrong choice, suggesting the coding of the history of negative outcomes. Notably, the wrong-type neurons included more aversive (42%) than appetitive (29%) and neutral (29%) type, while the correct type included more appetitive (40%) and neutral (40%) than aversive (20%) type. These results indicate the interacting nature of emotional and cognitive signals in single DRN neurons in specific temporal dynamics. The DRN may coordinate behavior under different moods through its widespread projections.

Disclosures: **M. Yasuda:** None. **Y. Ueda:** None. **K. Nakamura:** None.

Poster

699. Emotional States

Location: Halls A-C

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Program#/Poster#: 699.18/PP14

Topic: G.03. Emotion

Support: Institutional funds, Albany Medical College

Title: Virally-transduced deletion from locus coeruleus norepinephrine neurons suggests a role for glucocorticoid receptors in preventing depression-like behavior

Authors: *L. JACOBSON
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Abstract: Glucocorticoids can cause a variety of psychiatric symptoms including depression, anxiety, mania and psychosis that can be an obstacle to immunosuppressive glucocorticoid therapy and have been implicated in clinical mood disorders. Transgene-mediated glucocorticoid receptor (GR) deletion from all norepinephrine (NE) cells has been reported to increase depression-like behavior in female but not male mice, suggesting that GR may mediate mood-elevating effects in a sex-dependent manner. Such antidepressant-like actions could represent targets for treating depression, but the specific NE cells responsible for these effects have not been identified. I hypothesize that these antidepressant-like effects are mediated by locus coeruleus (LC) NE neurons, which express GR and are the primary source of NE in the brain. To test this hypothesis, I used lentiviral vectors (provided by Sergei Kasparov, Univ. of Bristol, UK) to transduce expression of Cre recombinase or green fluorescent protein in NE neurons of female floxed GR mice under the control of a multimerized Phox2 response (**PRS**) element (PRS-Cre or PRS-GFP, respectively). Bilateral LC injection of PRS-Cre produced complete GR deletion within 2 weeks that was limited to the LC. Female floxed GR mice with LC GR deletion exhibited significantly lower social interaction, a measure of depression-like avoidance behavior, compared to those receiving equivalent injections of PRS-GFP. There were no differences in non-social exploratory behavior between the groups. These results suggest that LC NE GR could

account for the depressive effects previously reported in female mice from transgenic deletion of GR from all NE cells, and indicate that LC NE GR can mediate mood-elevating effects of glucocorticoids. Such antidepressant-like actions could explain the contradictory array of potential psychiatric side effects from clinical glucocorticoid treatment and may represent novel targets for depression medication.

Disclosures: L. Jacobson: None.

Poster

699. Emotional States

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 699.19/DP12/PP15 (Dynamic Poster)

Topic: G.03. Emotion

Title: Transcriptional signatures of experience reveal Egr2 as a regulator of behavioral response to aversive stimuli

Authors: *B. M. IGNATOWSKA-JANKOWSKA[1], B. GONZALES[2], L. IZAKSON[2], D. HARITAN[2], C. COHEN[2], N. BLEISTEIN[2], A. TEREM[2], D. MUKHERJEE[2], E. ITZKOVITZ[2], H. TURM[1,2], A. CITRI[1,2]
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Abstract: Our previous studies revealed unique transcriptional patterns of immediate early gene (IEG) induction in specific brain regions that characterize distinct experiences. Robust transcriptional programs were identified, and dramatic differences were revealed in the encoding of aversive (LiCl, foot shock) vs rewarding (cocaine, sucrose) experiences so that a signature of a handful of IEGs was sufficient to decode the recent experience of individual mice with over 90% accuracy. In response to aversive experiences, we have identified a group of IEGs, including *Fos, Arc, Egr2* showing characteristic strong induction in the Amygdala as well as other components of the Extended Amygdala formation. We hypothesized that specific and selective IEG induction that we observed, plays a role in altering behavior in response to aversive experiences that produce their transcription. In order to test the role of IEG induction in response to aversive experiences, we aimed to determine whether selective and local suppression of this induction will alter behaviors associated with aversive experiences that induce their expression. We have suppressed the activity of the most prominently induced IEG, *Egr2*, through viral adeno-associated virus transfection of short hairpin RNA (shRNA) (n=8) as well as dominant negative (DN) mutation antagonistic to the gene product (n=8). This manipulation suppressing *Egr2* gene activity resulted in a behavioral change of coping strategy of mice as compared to animals injected with the control virus (n=8). We have found that inhibition of the *Egr2* that is robustly induced by aversive experience caused increased conditioned place aversion

response to LiCl, decreased freezing in response to footshock but shortened latency to escape environment associated with shock. Moreover, animals subjected to these manipulations showed higher activity and spent less time immobile during forced swim test, as compared to controls. This indicates that suppression of *Egr2* affects behavioral coping strategy in response to aversive stimuli, shifting it towards active coping - including an increase in locomotor activity and promoting avoidance and escape behaviors. The mechanism through which *Egr2* affects behavior and the role of *Egr2*-expressing neuronal ensembles remains to be unraveled. Our results indicate that unique transcriptional patterns characterizing experiences reveal new roles of IEGs in altering behaviors in response to experience that induced their transcription. This approach will help to identify new genes and neuronal ensembles allowing to manipulate behavioral response as well as unravel its underlying mechanisms.

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Poster

699. Emotional States

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 699.20/PP16

Topic: G.03. Emotion

Support: Brain & Behavior Research Foundation (2014 Narsad Young Investigator Grant #22487)

Title: Activation of basolateral nucleus of the amygdala on dopamine activity in behaving rats

Authors: *C.-W. LAI, C.-H. CHANG
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Abstract: Basolateral nucleus of amygdala (BLA) is responsible for processing negative emotions, but the relation between BLA and dopamine (DA) reward system is largely unclear. The number of spontaneously firing DA neurons, which is defined as “population activity” in ventral tegmental area (VTA), decides the amplitude of DA response to external stimuli. Previous electrophysiological studies have shown that rats that underwent chronic mild stress or acute restraint stressor resulted in an attenuation of DA population activity, which is restored with blockade of BLA activity. In this study, we aimed to examine how BLA activation impacts DA population activity and related negative emotions in rats. DA neuron population activity was assessed by the behavior responses of the animal to psychostimulant, amphetamine (AMPH); several studies have shown that the level is positively correlated with the AMPH-induced increase in locomotor activity. Negative emotional states were explored with elevated plus maze

(EPM; anxiety-like behavior) and forced swim test (FST; despair-like behavior). BLA was pharmacologically activated with N-methyl-D-aspartate (NMDA, 0.75µg/0.5µl per side) or vehicle control (VEH) before each of the behavioral assays. Our preliminary results suggest that after acclimation to the open field arena (30 min), systemic injection with AMPH (0.5mg/kg, i.p.) significantly increase the locomotor activity (total travel distance in 90 min), which was dampened with BLA activation. Compared to VEH controls, animals showed a trend of increase in the time spent in open arms (5 min test) in EPM (decreased anxiety) and decrease in immobility (5 min test) in FST (decreased despair). Our preliminary data suggests that under BLA activation, these animals were in an anxiolytic state but at the same time displayed dampened DA population activity, as if they were less anxious but also less responsive to potential reward stimuli. More work is in progress to confirm the conclusion.

Disclosures: C. Lai: None. **C. Chang:** None.

Poster

699. Emotional States

Location: Halls A-C

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Topic: G.03. Emotion

Support: JSPS KAKENHI Grant Number 24700423

JSPS KAKENHI Grant Number 16K21509

Title: Neuronal activity related to preference of visual stimuli in monkey amygdala

Authors: *K. KURAOKA[1,2], M. INASE[2]
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Abstract: Visual stimuli can serve as positive or negative reinforcer for nonhuman primates even though those stimuli are not accompanied with fluid reward or aversive punishment. Especially, social stimuli that are visually presented attract much interest of nonhuman primates. One of candidates for neural substrate processing social value conveyed by visual information is the amygdala that is known to respond to social stimuli and reward. To elucidate the involvement of the amygdala in processing sociality-related visual information, we recorded the activity of neurons in the monkey amygdala while an arbitrary geometric pattern was associated with one of the subsequent visual images of conspecifics or fluid reward. Behavioral data showed that the subject monkeys preferred images of the opposite sex, while they avoided the negative facial expressions of others. Of the recorded 173 neurons in the macaque monkey amygdala, 42 (24%) and 39 (23%) neurons showed excitatory and inhibitory responses to at least one of sociality-

related visual stimuli, respectively. A two-thirds (28/42, 67%) of neurons that showed excitatory responses to the visual stimuli also responded to fluid reward. The population activity of these neurons in response to preferred visual stimuli was significantly stronger than that in response to unprefered visual stimuli. To estimate how well individual neurons discriminate the monkeys' preference of visual stimuli, we conducted an ROC curve analysis comparing neuronal responses to between the preferred and unpreferred visual stimuli, and calculated an area under the curve (AUC). The AUCs of neurons showing excitatory responses were significantly higher than 0.5 which is indifferent point between two populations. In contrast, the AUCs of neurons showing inhibitory response were not different from 0.5. These results mean that only neurons showing excitatory responses detect the value difference of the visual stimuli. We also computed the temporal change of the mean AUC in the neurons showing excitatory responses. Results showed that the AUC transiently elevated just after presentation of visual stimuli. These results indicate that neurons showing excitatory responses in the monkey amygdala convey information of the value of visual stimuli.

Disclosures: K. Kuraoka: None. **M. Inase:** None.

Poster

699. Emotional States

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 699.22/PP18

Topic: F.02. Behavioral Neuroendocrinology

Support: ImmunoSter Corp

Title: Distribution of functional serotonin receptors in relation to the dopaminergic system

Authors: N. M. WLODARSKI[1], A. M. MITZEY[2], *M. S. BROWNFIELD[3]
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Abstract: Serotonin and dopamine mechanisms are both important factors in neuropsychiatric disease separately or togther through their release of neurotransmitters and interactions with other neurotransmitters in specific areas of the brain. Serotonin
affects feeding, mood, and social behavior, and is believed to interact with dopamine, a neurotransmitter affecting reward and addictive related behaviors. Dopaminergic pathways arising from the substantia nigra, ventral tegmental area and paraventriclar and arcuate nuclei project to the caudate nucleus, ventral forebrain, periaccubmens area, and hypothalamic sites. We question whether serotonergic and dopaminergic systems might affect each others' activities by cross communication or simply project specifically, directly and separately to important behavioral sites. To test the cross communication hypothesis we expect that specific serotonin

receptors are expressed by dopamine neurons. If the second hypothesis holds true then we should find serotonin receptors within and around the dopaminergic projection sites. To test these hypotheses we employed double immunofluorescence microscopy to map the distribution of serotonin agonist induced cfos expression in combination with localization of dopamine neurons by targeting its biosynthetic enzyme tyrosine hydroxylase. We administered 5HT1a, 5HT2a, 5HT2c, 5HT4, 5HT6, and 5HT7 selective agoinsts singly to Sprague-Dawley rats and studied induced fos expression in relation to dopaminergic neurons and terminals.Results failed to show functional 5HT receptor exception by dopamine neurons, exceptor for rare fos positive tyrosine hydroxylase cells. In contrast, dopamine terminal targets or closely adjacent structures contain dense expression of each of the 5HT receptors we tested.
These results favor the direct selective independent projection of dopaminergic and serotonergic systems to target sites.
Because evidence shows that disorder of these pathways may lead to Parkinson's disease, attention deficit hyperactive disorder, obsessive-compulsive disorder and addiction, or more, we can infer that serotonin receptor activation and specific dopamine neurons interact at brain behavioral sites, not by direct serotonergic modulation of dopaminergic activity. Whether the reverse may be true remains to be investigated.

Disclosures: **N.M. Wlodarski:** A. Employment/Salary (full or part-time):; None/Undergrad student, University of Wiscosnin. 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.; None. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); None. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); None. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); None. F. Consulting Fees (e.g., advisory boards); None. **A.M. Mitzey:** A. Employment/Salary (full or part-time):; Research Specialist$40K, University of Wiscossin. 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.; None. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); None. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); none. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); None. F. Consulting Fees (e.g., advisory boards); None. **M.S. Brownfield:** A. Employment/Salary (full or part-time):; Unv Wisconsin!emeritus!4). 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.; None. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Immunostar Corp. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); None. F. Consulting Fees (e.g., advisory boards); Consultant.

Poster

699. Emotional States

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 699.23/PP19

Topic: F.02. Behavioral Neuroendocrinology

Support: SSHRC Insight Development Grant

Title: Bridging the gap between pro-environmental concern and behaviour: The role of biological and psychological facets of learned helplessness

Authors: *N. R. LANDRY[1], T. MILFONT[2], A. C. WEEKS[1], R. GIFFORD[3], S. ARNOCKY[1]
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Abstract: Previous research has identified a gap between pro-environmental concern and behaviour, such that many concerned individuals nevertheless refrain from engaging in meaningful pro-environmental action. This has sparked calls for further study of psychological barriers to action. The present study proposes that psychological and endocrinological facets of learned helplessness may act as one such barrier. In a sample of 437 young Canadian adults, we examined the roles of trait learned helplessness and basal cortisol in moderating the concern - behaviour relationship. Results showed that learned helplessness moderated links between environmental concern and self-reported pro-environmental behaviour (B = -0.23, SE = .08, p = .004), as well as in-vivo measure of making a monetary donation to an environmental organization (B = -0.78, SE = 0.29, p = .007), and joining an on-campus environmental activism group (B = -0.62, SE = 0.30, p = .03). Individuals high in cortisol reported engaging in less self-reported pro-environmental behaviour (B = -0.24, SE = 0.11, p = .02). Cortisol also moderated links between concern and support for geo-engineering initiatives (B = -0.26, SE = 0.08, p = .001). Taken together, these results suggest that psychological and endocrine facets of learned helplessness act as barriers to pro-environmental behaviour in the face of environmental concern.

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Poster

700. Emotional States: Empathy

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 700.01/PP20

Topic: G.03. Emotion

Support: ERC-StG 312511

Title: Exploring possible cortical brain regions involved during the experience and observation of pain in mice

Authors: *R. BRULS[1], M. CARRILLO[1], K. L. KOOIJ[2], A. ROMAGUERA ÁLVAREZ[3], N. JELINEK[4], V. GAZZOLA[1], C. KEYSERS[1]
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Abstract: Mirror neurons, neurons that are activated both during the self-experience and observation of emotions, are thought to underlie empathic responses, which allow humans to share and understand emotions in others. Although human fMRI data has provided indirect evidence for regions involved in emotional mirroring, these techniques do not have the spatial or temporal resolution to answer questions at the cellular level. Rodents possess the fundamental attributes of empathy, and allow for the examination and understanding of neural mechanisms of empathy, at multiple levels. So far the main focus has been on the anterior cingulate cortex, a region involved in the pain matrix and hypothesized to contain mirror neurons for emotions in rodents. From human results, we know that there are various other cortical regions that are part of the empathy network, such as the somatosensory cortex. In this study, we investigated a broad range of cortical regions to explore other possible areas involved in the neural mechanisms of empathy for pain in mice. For this we combined widefield fluorescence imaging with the clear skull technique. Widefield fluorescence imaging is a powerful technique that allows measuring neuronal activity of the whole cortex at once. Several experiments were conducted in Thy1-GCaMP6 5.17 mice focusing on the self-experience and observation of pain. For the observation of pain, shock-experienced observer mice witnessed familiar demonstrators experience painful footshocks. For the self experience of pain, observers received painful footshocks, both when anesthetized and awake. Additionally, a fear conditioning task was performed consisting of the playback of a tone previously associated to shock onset to the observer. During all tasks, changes in fluorescence (delta f/ f) were recorded from the cortical surface of observer animals. Results show a widespread activation over the whole cortex during the self experience of pain while awake. This response is suppressed when mice are under anesthesia. When observing a conspecifc in pain, the activation pattern is reduced even more so, but still present, although

highly variable among mice. When examining areas more closely that are hypothesized to be involved in the empathy network (such as the somatosensory cortex, motor cortex and ACC) we find these areas to increase their activation pattern compared to baseline period, for the self experience and observation of pain.

Disclosures: R. Bruls: None. **M. Carrillo:** None. **K.L. Kooij:** None. **A. Romaguera Álvarez:** None. **N. Jelinek:** None. **V. Gazzola:** None. **C. Keysers:** None.

Poster

700. Emotional States: Empathy

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Topic: G.03. Emotion

Support: UFSCar

CNPQ (309201/2015-2)

FAPESP (2015/0006-4; 2015/11908-9)

Title: Empathy for pain: Alteration of hormonal levels and serotonergic and dopaminergic neurotransmission within amygdala and insula in mice living with a conspecific in chronic pain

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Abstract: AIM: We have recently shown that mouse living with a conspecific suffering with chronic pain [e.g., pain induced by sciatic nerve constriction (SNC)] displays increased nociceptive responses assessed with the writhing test. Furthermore, previous findings have shown the modulatory role of oxytocin, testosterone and corticosterone in empathy responses. Here, we investigated whether living with a conspecific suffering with chronic pain changes plasma oxytocin, testosterone, corticosterone and serotonin and dopamine turnover in the amygdala and insula in cagemates mice. **METHODS AND RESULTS:** Male Swiss mice (n=8-11 per group) were housed in pairs for 28 consecutive days. On day 14th, pairs of mice were grouped as follow: cagemate nerve constriction (CNC; i.e. one animal from each pair was subjected to SNC surgery) or cagemate sham (CS; i.e. one animal from each pair was subjected to SNC sham surgery). After that, each pair was returned to its homecage to live together for further 14 days. In Experiment 1, on testing day (day 28th), the observer cagemates were subjected to the writhing test. In Experiment 2, the cagemates were sacrificed and plasma

oxytocin, testosterone and corticosterone levels quantified through ELISA Kits. In Experiment 3, the cagemates were sacrificed and their brains removed for analysis of the serotonin and dopamine levels in the amygdala and insula through the high performance liquid chromatography (HPLC). Student *t*-test revealed that the CNC group displayed higher number of abdominal writhes ($t(14)=5.83$; $P< 0.05$), lower levels of testosterone ($t(12)=2.88$; $P< 0.05$), higher levels of oxytocin ($t(14)=-3.19$; $P< 0.05$), increased dopamine ($t(14)=-2.31$; $P< 0.05$) and serotonin ($t(17)=-2.59$; $P< 0.05$) turnover in the amygdala compared to the CS group. For the insula Student t-test revealed the increased of dopamine turnover ($t(18)=-2.59$; $P< 0.05$), but not significant effects for the serotonin turnover ($t(18)=0.01$; $P>0.05$). Student *t*-test did not reveal significant effects for corticosterone levels ($t(12)=-2.42$; $P>0.05$). **CONCLUSIONS:** These results demonstrate that living with a mouse subjected to SNC induces hyperalgesia, reduction of testosterone, and increased of oxytocin levels in the observer cagemate. In addition we observed the accentuation of dopaminergic and serotonergic turnover in amygdaloidal complex and the increased of dopaminergic turnover in the insular cortex. Taken together, the present results suggest that the plasma testosterone, oxytocin, dopamine and serotonin neurotransmission plays a role in the modulation of pain empathy in mice.

Disclosures: A. Canto-de-Souza: None. **D. Baptista-de-Souza:** None. **I. Carmona:** None. **C.R. Zaniboni:** None. **R.L. Nunes-de-Souza:** None.

Poster

700. Emotional States: Empathy

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 700.03/PP22

Topic: G.03. Emotion

Support: NSFC61627808

Title: Neural mechanisms of emotional contagion behavior in rats

Authors: *Z. WANG, C. ZHENG
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Abstract: Abstract Empathy is thought to be an advanced capability in human, which allows the individual to comprehend other's feelings by taking a stand on others. Recently, rodents have been successfully used in studying empathy-related behavior. Since the new technologies, such as optogenetics, chemogenetics, multi-channel electrode recording and fMRI, can be readily used in rodents, we could now study the mechanism of empathy-related behavior in a more thorough way. We employ the strategy of small animal functional magnetic resonance imaging (fMRI), to identify the specific brain region related to emotional contagion— the primary empathy in rodents. First, we are establishing an emotional contagion paradigm for rats which is compatible

in MRI. The brain activities of demonstrator and observer rats will be recorded and analyzed. After the emotional contagion-related brain regions are confirmed, we will trace the neural circuit through viral labeling and tracing to identify their downstream and upstream. Optogenetic or chemogenetic techniques will be used to manipulate the activities of the components in emotional contagion neural circuits in order to demonstrate the causality of their activities to the behavior.

Disclosures: Z. Wang: None. **C. Zheng:** None.

Poster

700. Emotional States: Empathy

Location: Halls A-C

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Program#/Poster#: 700.04/PP23

Topic: G.03. Emotion

Support: Pew Charitable Trusts Latin American Fellowship

ONR MURI Grant N000141310672

Title: Understanding the neural basis of empathy in rodents

Authors: *M. CONTRERAS[1], A. HATFIELD[1], J. CUMMINGS[1], K. CRUZ[2], J.-M. FELLOUS[1]
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Abstract: There is increasing support for the idea that empathy is evolutionarily conserved and shared across mammalian species. This suggests that the neurophysiological mechanisms of empathy, currently unknown, might be elucidated using an animal model. Previously, we have shown that rats exhibited empathic responses to conspecific distress while they performed an operant task, which seems to capture some of the natural individual differences observed in human empathy. Moreover, we have shown that the pharmacological manipulations of the oxytocin system altered some of the empathic responses observed during the task. The current study extends this work by assessing the role of arginine vasopressin system in rat empathy. Animals were trained to obtain food pellets by pressing either one of two cued levers in an operant chamber. During the empathy test, one of the levers was programmed to also deliver a footshock (0.5 mA, 0.5 sec) to a conspecific animal which was placed in full view, in an adjacent chamber. Single lever (forced-choice trial) or both levers (free-choice trial) were cued throughout the course of testing. We observed that intracerebro-ventricular administration of an antagonist of arginine vasopressin disrupted the expression of empathic responses. We further explore the involvement of the insular cortex, a region that has been associated with human empathy, in empathic responses exhibited by rats. Previously, we have shown that the neural

activity of the anterior insular cortex decreased during the empathy test. In this study we conducted several additional analyses to better understand the participation of the insular cortex in empathy. We also explore the role of 22 kHz ultrasonic distress vocalizations and social context and the extent to which they are necessary or sufficient for the expression of empathic-like responses. This research may have implications for the treatment of empathy deficits and related anti-social behaviors.

Disclosures: M. Contreras: None. **A. Hatfield:** None. **J. Cummings:** None. **K. Cruz:** None. **J. Fellous:** None.

Poster

700. Emotional States: Empathy

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 700.05/PP24

Topic: G.02. Motivation

Support: Oslo and Akershus University College - Strategy funding from the R&D committee

Title: Rodent model of Empathy: Rats employ taught behavior to help cagemate that remains intact during environmental change

Authors: *M. H. BLYSTAD, D. ANDERSEN, E. B. JOHANSEN
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Abstract: In Social Neuroscience, empathy has received increased attention during the last decades. Animal models are emerging as possible venues for further probing of the mechanisms of empathy (Keum & Shin, 2016), but much work remains. This study uses the pro-social helping paradigm originating from Bartal, Decety, and Mason (2011) in which one rat is taught to release a trapped cagemate from a restrainer (Illustration 1). The original findings implicate empathic distress as a possible motivator for rodent helping behavior. However, in the original studies, the rats were trained in the same situation as used for pro-social testing. We wanted to investigate whether training of door opening with food reward affected door opening with a trapped cagemate.
We also measured ultrasonic vocalizations (USV) of the rats. USVs play a large role in social-emotional communication (Brudzynski, 2013), and the influence of USVs are largely unknown in pro-social experiments. Thus, the present study investigated the association between positive USVs and pro-social situations.
In experiments on environmental change, all rats were trained and tested for pro-social behavior in a highly illuminated setting ("bright", 200-400 lux), and tested again in an almost pitch black setting ("dark", ≥2 lux).
Our results support the findings from Bartal et al., (2011): 1) Rats will act pro-socially towards

cagemates, and, 2) Rats will not open the door/show much longer latency, when the restrainer is empty. Prior door opening training produced much faster pro-social behavior than in the original study (1 day vs ≈ 7). No effect of changing illumination from bright to dark, or vice versa, was found on pro-social behavior. Finally, preliminary analysis of positive USV's show no systematic influence on pro-social behavior.

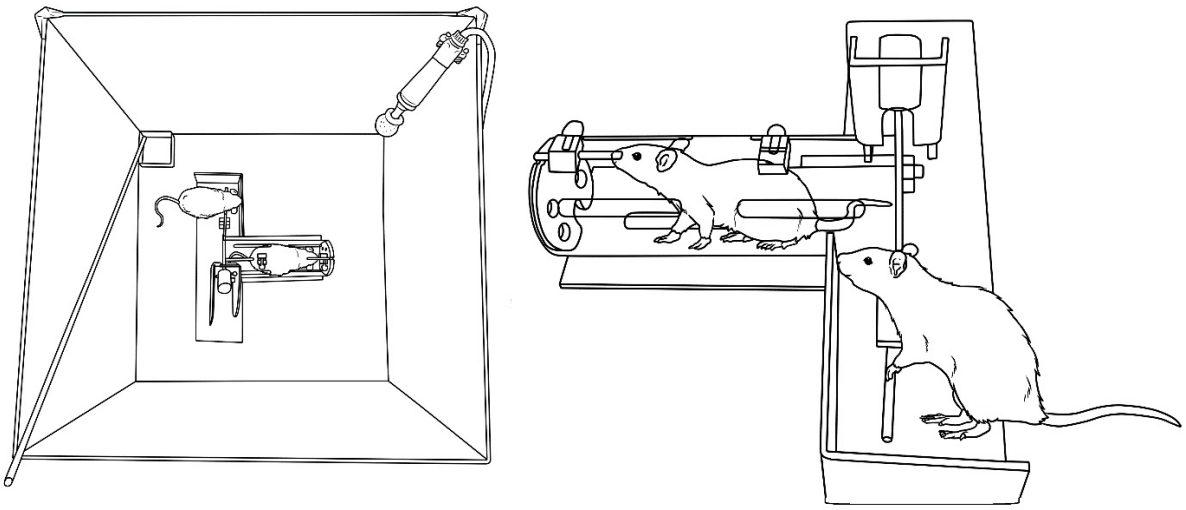

Illustration 1 Above left: The arena with restrainer and opening mechanism. On the left wall is a pipe extending outside of the arena for administration of food pellets during training. In the top right corner a microphone is attached for recording of USVs. Above right; detailed view of opening mechanism.

Disclosures: M.H. Blystad: None. **D. Andersen:** None. **E.B. Johansen:** None.

Poster

700. Emotional States: Empathy

Location: Halls A-C

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Program#/Poster#: 700.06/PP25

Topic: G.03. Emotion

Support: NIH Grant EY022157

Title: Parsing the neural circuits for visual empathy

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Abstract: The ability to perceive and respond appropriately to the emotions of others is fundamental to social interactions and our evolution as a species. This process relies on an

integration of sensory perceptions and emotions, but where in the brain that merging occurs is unknown. Moreover, the failure of that circuitry to function properly likely underlies various developmental disorders of cognition, such as autism spectrum disorder. Despite a considerable number of studies exploring the neural correlates of empathy in humans and non-human primates, we still understand little about the cell types, circuit architecture, and computations that allow for empathy.
As a first step to remedy that, we developed a behavior paradigm in mice in which they view other members of their species engaged in visual fear (Yilmaz and Meister, 2013; Salay et al., in preparation) and asked:
1) Can mice visually determine the emotional state of their conspecifics?
2) What behavioral repertoires do the observer mice perform?
3) What are brain areas causally linked to this feature of 'visual empathy'?
We found that observer mice display empathic behaviors after observing a series of defensive reactions in conspecifics (demonstrators) who are under an immediate visual threat. Molecular genetic exploration for the neurons that read out visual empathy revealed a novel subset of subcortical and cortical nuclei implicated in this form of sensory-emotional integration and cognitive control. To parse the anatomical and functional roles of these identified brain regions, we are applying viral tracing as well as optogenetic and chemogenetic control over neural activity in the context of our 'empathy' assays. Our results provide evidence that the ability to relate to the emotional state of others exists in rodents and may have a common neural substrate.

Disclosures: H. Jung: None. **A.D. Huberman:** None.

Poster

700. Emotional States: Empathy

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 700.07/PP26

Topic: F.02. Behavioral Neuroendocrinology

Support: UConn IDEA Grant

UConn IBACS Grant

Title: "Observational learning: Comparing a foraging and aversive motivated task in female rats"

Authors: *R. TROHA, D. DONG, T. PIETRUSZEWSKI, A. AGRAWAL, K. MATHEW, N. HERNANDEZ, E. MARKUS
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Abstract: Observational, or imitative, learning is a vital skill for survival. This type of social learning plays an important role in human development (e.g. Bandura) but is also relevant for

other species. Learning from the trial and error of others is more efficient than searching yourself when foraging the environment for food. It is also "safer" to acquire information regarding locations of danger in the environment by watching where conspecifics are threatened and how they may/may-not escape the danger.
We have developed an observational learning paradigm in which rats observe the solution in a T-shaped maze. This is a working memory task with the correct goal changing on a daily basis. Therefore, the observer must attend to the demonstrator rat's performance on a daily or continuous basis.
As noted above, there are two types of circumstances in which observational learning can facilitate survival. The first is escaping an aversive situation, such as observing which behaviors prevented predation and which did not. The second is using observation to facilitate food seeking success (e.g. where other members of the species are finding food).
For the escape situation, 8 female F344 rats were trained on a T-shaped maze submerged in water. Animals were placed at the stem of the T-maze and needed to navigate to the arm containing the escape platform on that day.
For the foraging task, a different group of 8 female F344 rats were used. These animals were placed on a T-maze with a food reward at the end of one arm.
In both paradigms the goal location varied across days and the animals had the opportunity to observe a conspecific perform the correct response. Performance was related to number of exposure trials, identity of the observer, identity of the demonstrator, and effects of the estrous cycle.
Funding: UConn IDEA Grant, UConn IBACS
Keywords: Observation, social, learning, behavior
Theme: F.02.c Social behavior

Disclosures: R. Troha: None. **D. Dong:** None. **T. Pietruszewski:** None. **A. Agrawal:** None. **K. Mathew:** None. **N. Hernandez:** None. **E. Markus:** None.

Poster

700. Emotional States: Empathy

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 700.08/PP27

Topic: G.03. Emotion

Title: Effects of placebo analgesia on the multi-voxel representations of directly experienced pain and pain empathy

Authors: *I. WAGNER, M. RÜTGEN, C. LAMM
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Abstract: Empathy for pain engages similar brain regions as a direct, painful experience. This suggests common representations for the two experiences that appear anchored in mid-cingulate and anterior insular cortices (MCC, AI). Definitive evidence for such common representations is, however, missing. We recently demonstrated that placebo analgesia reduces both pain empathy and self-pain (Ruetgen et al., 2015). Here, we re-analyzed the fMRI data of this study. We used multi-voxel pattern analysis (MVPA) to investigate the neuronal representations of pain empathy and self-pain and how they were affected by placebo analgesia.
Participants (placebo/control group, *N*=49/53) underwent fMRI while receiving painful and non-painful electrical stimulation, or when observing another person being exposed to such stimulation. MVPA primarily focused on MCC and AI was used to test representations of self- and other-directed stimulation (pain/no pain), and common or distinct representations between self- and other-directed stimulation (self/other).
We found that MCC and AI representations of self-directed stimulation partly generalized to other-directed stimulation and vice versa. Self- and other-directed painful and non-painful stimulation were dissociable in the control group, but this was not possible for other-directed stimulation in the placebo group. Initial whole-brain searchlight results point towards altered prefrontal control processes following placebo analgesia.
In conclusion, placebo analgesia appears to change neuronal representations that underlie direct pain and pain empathy.

Disclosures: I. Wagner: None. **M. Rütgen:** None. **C. Lamm:** None.

Poster

700. Emotional States: Empathy

Location: Halls A-C

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Topic: G.03. Emotion

Support: NIH Grant DA040717

NIH Grant MH107444

Medoc Advanced Medical Systems USA

University of Maryland

Title: Anxiety, pain, and cognition are integrated in the brain

Authors: *M. D. STOCKBRIDGE[1], A. J. FURMAN[5], M. L. KEASER[2], J. S. PAYANO SOSA[5], S. PADMALA[3], A. S. FOX[6], L. PESSOA[4], J. F. SMITH[4], D. A. SEMINOWICZ[2], A. J. SHACKMAN[4]
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Res. and Dept. of Neural and Pain Sci., Univ. of Maryland, Baltimore, MD; [3]Neurosci. and Cognitive Sci. Program, [4]Psychology, Univ. of Maryland, College Park, MD; [5]Neurosci. Program, Univ. of Maryland Sch. of Med., Baltimore, MD; [6]Psychology, Univ. of California - Davis, Davis, CA

Abstract: The rostral cingulate cortex lies at the heart of neuroscientific models of emotion, pain, and cognitive control. Work in these three basic domains has, in turn, profoundly influenced contemporary perspectives on more complex phenomena, including social processes and psychopathology. Yet, key questions about the functional organization and significance of activity in the rostral cingulate remain unresolved. Perhaps the most basic question is whether emotion, pain, and cognitive control are segregated into distinct subdivisions of the cingulate or are integrated in a common region, with recent reports providing conflicting answers. Here, we used a combination of brain imaging techniques—including large-scale meta-analyses and high-resolution analyses of individual subjects—to provide converging evidence that negative affect, pain, and cognitive control recruit an overlapping region of the anterior midcingulate cortex (MCC). 'Automated' meta-analyses were performed using computer-generated databases (70-478 studies) and NeuroSynth (q<.01). 'Gold standard' meta-analyses were performed using manually curated databases (43-90 studies) and GingerALE (p<.05). Our results show that meta-analyses performed using different databases and different analytic approaches revealed three-way overlap in the MCC, suggesting that this effect is both reproducible and generalizable. Nevertheless, it is well known that such meta-analyses entail an enormous loss of spatial resolution, which can create spurious regions of overlap. To address this, fMRI data were acquired from 23 individuals while they completed tasks that elicited negative affect (threat-of-shock), induced pain (hot thermal stimulation), or demanded cognitive control (MultiSource Interference Task). To maximize resolution, data were normalized using diffeomorphic techniques. Results revealed three-way overlap in anterior MCC, both for spatially smoothed (6-mm) and unsmoothed data (qs<.05). A final set of analyses focused on spatially unsmoothed, single-subject data. This demonstrated that a higher proportion of subjects showed multi-task overlap in MCC compared to a control region, both for smoothed and unsmoothed data (ps<.001). The extent of multi-task overlap also was greater in MCC versus the control region (ps<.004). In sum, negative affect, pain, and cognitive control show substantial overlap in MCC—even for high-resolution data examined in individual subjects. Collectively, these results provide a new, neurobiologically grounded framework for understanding the contribution of the MCC to a broad spectrum of psychological processes and psychiatric disorders.

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Poster

700. Emotional States: Empathy

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 700.10/PP29

Topic: G.03. Emotion

Title: Neurophysiology of emotional reactivity from a corpus of affective speech: Theory of mind and referential proximity

Authors: *F. ISEL[1], A. LACHERET-DUJOUR[2]
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Abstract: Previous event-related brain potentials (ERPs) using IAPS pictures have shown that emotional reactivity is often associated with the late positive potential (LPP). Few studies have examined emotional reactivity from an affective speech. In the perception of an emotion expressed linguistically, the theory of mind, i.e., the ability to represent the emotional state in question can be mobilized to different degrees. It depends on whether the referent designated by the agent and/or the patient of the event that causes him a particular emotional state are referentially related, if not identical to the speaker who reports the event. In the present ERP study, we aimed to test this issue. For this purpose, we constructed 320 French sentences including 120 sentences with positive valence, 120 with negative valence and 120 with a neutral valence. In half of the sentences the referent designated by the agent and/or the patient of the event that causes a particular emotional state were referentially related to the speaker (a) « C'est avec cet objet que le crâne de mon père a été fracassé. », *It is with this object that the skull of my father was shattered*), while in the other half not (b) « C'est avec cet objet que le crâne d'un homme a été fracassé. », *It is with this object that the skull of a man was shattered*). We hypothesized that if the theory of mind is activated, then the empathy of the individual perceiving the emotion should be larger in (a) than in (b). This should be reflected by an enhancement of the LPP. While the effect of referential proximity gave a consistent picture in the behavioral data with a stronger emotional impact for sentences with a close referential proximity, unexpectedly a reduced LPP was found for these sentences. The present findings suggest that emotional sentences, in the same way to IAPS pictures, may constraint differently emotional states. Moreover, and more importantly, our data supported the prediction that linguistic material creating a particular emotional state because of referential proximity was able to modulate the LPP amplitude.

Disclosures: F. Isel: None. **A. Lacheret-Dujour:** None.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 701.01/QQ1

Topic: G.05. Anxiety Disorders

Support: Research Project Grant A by Institute of Science and Technology Meiji University

Title: Hatano rats suitable as metabolic syndrome model focusing on feeding behavior and physiological strain differences

Authors: A. ISOBE[1], G. SHIMAZAKI[1], T. SAKAWA[2], T. SHIMADA[3], M. ABURADA[4], T. NAKAMURA[2], R. OHTA[5], M. KAWAGUCHI[1]
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Abstract: Metabolic syndrome refers that the abdominal circumference is over a certain size and at least two of the three following conditions are also met; 1. High blood pressure, 2. High plasma glucose level, 3. Dyslipidemia. It is closely linked to leading causes of death like heart disease and cerebrovascular disease, affecting many people worldwide. Some studies have reported that stress can effect eating patterns and appetite, and that stress eating can cause metabolic syndrome. Therefore, the risk of metabolic syndrome can be related to stress response and stress sensitivity. Although many studies have established metabolic syndrome models, there are few models focusing on stress response and stress sensitivity. Therefore, it is important to establish a metabolic syndrome model focusing on stress. In this study, we used Hatano high-avoidance animals (HAA) and low-avoidance animals (LAA) that were derived from Sprague-Dawley rats by selectively breeding for high and low avoidance rates in shuttle-box active avoidance tests. Some previous studies have shown that HAA shows higher stress response and higher stress sensitivity than LAA. Also, there are endocrinological stress differences, for example, LAA shows higher corticotropin-releasing hormone levels in the paraventricular nucleus than HAA. However, the strain difference on feeding behavior has not been clarified. Given that stress is related to eating and appetite, it is assumed that there could also be a strain difference in feeding behavior between HAA and LAA. In this study, we determined whether the stress related endocrinological differences between the Hatano rat strains could be useful for a metabolic syndrome model. We examined food intake, blood pressure, plasma component levels and animal fat contents. HAA rats had more active feeding behavior, higher blood pressure, higher percent fat and higher triglyceride levels than LAA rats. These features of the HAA rats correspond to some of the metabolic syndrome symptoms. Therefore, it suggests that HAA can be used as a metabolic syndrome model focusing on stress response and stress sensitivity. This

study was supported by Research Project Grant A by Institute of Science and Technology Meiji University.

Disclosures: A. Isobe: None. **G. Shimazaki:** None. **T. Sakawa:** None. **T. Shimada:** None. **M. Aburada:** None. **T. Nakamura:** None. **R. Ohta:** None. **M. Kawaguchi:** None.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 701.02/QQ2

Topic: G.05. Anxiety Disorders

Title: Previous inescapable stress interferes with the immunizing, but not the acute, effect of later escapable stressors

Authors: *K. L. BARTHOLOMAY, S. TILDEN, J. AMAT, L. WATKINS, S. F. MAIER
Dept. of Psychology and Neurosci., Univ. of Colorado Boulder, Boulder, CO

Abstract: For many years it has been known that behavioral control over an adverse event, referred to here as a stressor, can prevent the immediate behavioral and neurochemical impacts typically associated with an adverse event. Additionally, behavioral control has been shown to immunize, or protect, against the behavioral and neurochemical effects of future stressors, even in the absence of control. However, there are no previous studies that investigate the proactive impact that an initial experience of a stressor without behavioral control might have on the acute protection and immunization provided by future controllability. Here, a stressor over which the subject had no behavioral control was administered prior to a stressor which the subject could control in order to determine the impact on the acute and immunization effects typically associated with controllability. Behavioral results suggest that prior stressor exposure without the experience of control has no impact on the acute protection provided by future controllability, but blunts the ability of later control to immunize against future adverse events. Clinically, these results imply that prior trauma may impact the ability to reestablish behavioral control over future stress, which may prevent trauma survivors from developing resistance or resilience to cope with stress via behavioral control.

Disclosures: K.L. Bartholomay: None. **S. Tilden:** None. **J. Amat:** A. Employment/Salary (full or part-time):; University of Colorado Boulder. **L. Watkins:** A. Employment/Salary (full or part-time):; University of Colorado Boulder. **S.F. Maier:** A. Employment/Salary (full or part-time):; University of Colorado Boulder.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 701.03/QQ3

Topic: G.05. Anxiety Disorders

Support: Fred B. Snite Foundation

Title: SABV and the limitations of animal studies for addressing gender disparities in neurobehavioral health

Authors: *L. S. ELIOT[1], S. S. RICHARDSON[2]
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Abstract: Many brain and behavioral disorders differentially affect men and women. The new NIH requirement to include both male and female animals in preclinical studies aims to address such health disparities, but we argue that the mandate is a flawed approach to this problem. Sex differences are highly species-specific, tied to the mating system and social ecology of a given species or even strain of animal. Sex itself is complex phenotype, not the simple binary variable that this mandate assumes. In many cases, animal models poorly replicate male-female differences in brain-related human diseases such as depression, anxiety, and chronic pain disorders. Gender disparities in human health have a strong sociocultural component that is intimately entangled with biological sex and not addressed by this policy. We support research that investigates sex-related variables in hypothesis-driven studies of animal brains and behavior. We also support full transparency in reporting of animal sex in all scientific publications. However, institutional policies that give sex special salience over other sources of biological variance distort research. We further caution that the imposition of sex analysis on all animal research entrenches neuroscientists' presumption that gender differences are largely hormonal or genetic in origin and overlooks the powerful social, psychological and cultural contributors to male-female neuropsychiatric health gaps. Although well-intentioned, the new policy is unlikely to reduce gender disparities in human neurobehavioral health, while posing a large burden on basic scientists.

Disclosures: L.S. Eliot: None. **S.S. Richardson:** None.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 701.04/QQ4

Topic: G.05. Anxiety Disorders

Title: The anxiolytic-like effect of Montanoa tomentosa depend of endocrine condition

Authors: *E. M. ESTRADA[1], D. M. ISLAS-PRECIADO[2], I. SOLLOZO-DUPONT[3], C. LOPEZ-RUBALCAVA[4]
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Abstract: *Montanoa tomentosa* "zopatle" or "cihupatli" is a native plant of Mexico that has been used in traditional medicine mainly as a remedy for reproductive impairments and relaxing actions. Although females are the main users of this plant, there are no studies that evaluate the potential impact of the endocrine milieu that could affect its antianxiety actions. Therefore, the present work was conducted to assess the anxiolytic-like effects of *Montanoa tomentosa* (fam: Asteraceae) lyophilisate (MT) on female rats under different endocrine conditions. For this purpose, in experiment 1 intact young female Wistar rats in a condition of high (proestrus-estrus) - or low- (metestrus-diestrus) hormone levels and ovariectomized were treated with vehicle or MT and tested in the elevated plus-maze test (EPM). In experiment 2, the effect of MT was compared with diazepam in rats under progesterone withdrawal (PW) treatment schedule. Finally, in experiment 3, the participation of $GABA_A$ receptor in the anxiolytic-like action of MT was evaluated in ovariectomized female rats using picrotoxin as anantagonist to chloride ion channel. MT increased the time in open arms entries in female rats in a low hormone level condition and at low doses, MT-induced anxiety in rats tested in a high hormone level condition. MT-induced an anxiolytic-like effect in females under PW treatment schedule in contrast to diazepam that was ineffective. MT's anxiolytic-like effect was blocked by picrotoxin suggesting the participation of GABAA receptor complex.

Disclosures: E.M. Estrada: None. **D.M. Islas-Preciado:** None. **I. Sollozo-Dupont:** None. **C. Lopez-Rubalcava:** None.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 701.05/QQ5

Topic: G.05. Anxiety Disorders

Support: CONACyT grants No. 247243 and 247233 to JRE and CC, respectively.

VIEP-BUAP 2017

CA of Neuroendocrinología CA-BUAP-288

Title: Low-yawning line showed higher anxiety and depression respect to high-yawning and Sprague-Dawley rats

Authors: *J. EGUIBAR[1], C. CORTES[2], A. UGARTE[2], L. DIAZ[2], A. TRUJILLO[3]
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Abstract: High- and low-yawning (HY and LY, respectively) rats were obtained by strict inbreeding process for more than 80 generations. HY rats had more grooming bouts when exposed to novel environment or after wetting the fur and in the open-field arena (OFA) showed higher ambulation and less number of fecal boluses respect to low-yawning (LY) rats suggesting that HY are less emotionally reactive than LY rats. The aim of this study was to analyze the responses of HY, LY and Sprague-Dawley (SD) rats on the elevated-plus maze (EPM) to evaluate anxiety and using forced swimming test to measure depression.
We used 48 subjects (Ss, eight from each group of rats) which were maintained under standard animal room conditions and with free access to rodent pellets and purified water. Ss were under 12:12 light-dark cycle (lights on 0700), all experiments were done between 1000 to 1400 in a sound-proof room with a 300 lux illumination and the observer was blinded respect to group of rats tested. EPM and forced swimming test were done when rats were 100 days of age and both tests were recorded and analyzed using The Observer XT software (Noldus, Netherlands). All procedures followed the NIH rules and the protocol were approved by IACUC No. EGCJ-SAL-17-G.
Our results showed that in EPM HY explore more and had more vertical displacements (rearings + wall-leanings) than LY and SD rats. Additionally, HY had more entrances and spent more time in the open arms respect to obtained in LY and SD rats ($P \leq 0.05$). In forced swimming test HY rats showed more active behaviors: swimming and scaling than other two groups of rats ($P \leq 0.05$). On the opposite, LY subline showed higher immobility time respect the other rats ($P \leq 0.05$). In base of these results HY showed less anxiety trait, and lower depression because had more active behaviors particularly scaling and less diving to the bottom of the cylinder that

means scape. On the other hand, LY rats showed higher anxiety in EPM and depressive-like behavior in forced swimming test.
In conclusion, HY rats is a useful animal model to analyze the psychobiological basis of resilience to anxiety and depression and the change of these behaviors are probably due to the strong inbreeding process

Disclosures: **J. Eguibar:** None. **C. Cortes:** None. **A. Ugarte:** None. **L. Diaz:** None. **A. Trujillo:** None.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

Location: Halls A-C

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Topic: G.05. Anxiety Disorders

Support: Research Project Grant(A) bte of Science and Technology Mejy Institui University

Title: Contextual fear conditioning test in Hatano high and low avoidance rats

Authors: *T. OKAWARA[1], R. OHTA[2], T. INOUE[3], M. KUBONOYA[3], M. KAWAGUCHI[3]
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Abstract: Inbred strains of Hatano rats, high- (HAA) and low-avoidance (LAA) animals, have been selectively bred for high and low performance in a two-way shuttle-box active avoidance task. When compared to LAA rats, HAA rats show higher anxious behavior in the elevated plus maze, and show higher avoidance performance in passive avoidance test. These results suggest that there are strain differences in response to aversive stimulus. It is known that rats show freezing reactions to electric shocks, and also that they emit ultrasonic vocalizations (USV) at 22 kHz when they receive aversive stimuli, which reflect their negative state. We measured freezing responses and number of USV of Hatano and SD male rats in a fear conditioning test and a fear extinction test. In the fear conditioning test, the rats were put in a device that delivered electric shocks at regular time intervals. For the fear extinction test, the rats returned 24 hours later to the place where they received the electric shocks.The frequency of freezing responses was greater in both LAA and HAA rats compared to SD rats in the conditioning test. However, LAA rats showed lower freezing responses than HAA rats in the fear extinction test. Furthermore, there was no difference in total number of USVs in the conditioning test, but LAA showed lower number of USVs than SD and HAA rats in the fear extinction test. These results clearly suggest that HAA rats show greater memory to aversive stimuli than LAA rats. We will provide comparing the activities and size of brain areas related to these strain differences. Research Project Grant A by Institute of Science and Technology Meiji University.

Disclosures: **T. Okawara:** None. **R. Ohta:** None. **T. Inoue:** None. **M. Kubonoya:** None. **M. Kawaguchi:** None.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 701.07/QQ7

Topic: G.05. Anxiety Disorders

Title: Chronic stress-induced changes in parvalbumin cells of the prefrontal cortex contribute to increased anxiety in a sex-specific manner

Authors: *L. COUTELLIER[1], R. SHEPARD[1], K. HESLIN[1], C. PAGE[2]
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Abstract: Hypoactivity of the prefrontal cortex (PFC) has been well described in both humans and rodent models of stress-induced depressive and anxious behaviors. However its origin is unknown and its contribution to behavioral changes, specifically in females who have increased risk for stress-related mood disorders, remains poorly studied. We hypothesized that prefrontal hypoactivity following exposure to stress is the result of stress-induced changes in the prefrontal GABAergic system, and that these changes are predominant in females, providing a possible mechanism mediating sex differences in stress-related mood disorders. We previously observed that female mice exposed to unpredictable chronic mild stress (UCMS) in adulthood express higher levels of parvalbumin (PV) mRNA, and display increased number of PV interneurons (PV-I) in their prefrontal cortex (PFC), which was positively correlated with increased emotionality (including anxiety- and depressive-like behaviors). Our goals with the present study were (1) to determine whether the increase in PV in the PFC following UCMS is the result of stress-induced chronic activation of these cells leading to their state of hyperactivity even once UCMS ceased; (2) to establish a causal relationship between increased activity of prefrontal PV-I and increased emotionality in a sex-specific manner. To address the first point, we used double immunofluorescent techniques to measure the level of PV-I expressing cFos (as a measure of neuronal activity) following UCMS. We observed a significant increase in the number of PV-I in the PFC that express cFos at rest and under stimulated conditions, particularly in female mice. To address the second point, we used a chemogenetics (DREADD) approach. Chronic PV-I activation in the PFC leads to high anxiety in female mice, but not in males as measured in the open-field and novelty suppressed feeding tests, but do not induce changes in depressive-like behaviors, as measured in the forced swim test. Altogether, we conclude that chronic stress exposure can lead to an over active prefrontal PV system particularly in female mice, and that changes within this system are causatively responsible for increased anxious behaviors. This

heightened sensitivity of the prefrontal PV system in females could explain increased risk of females to stress-related mood disorders.

Disclosures: **L. Coutellier:** None. **R. Shepard:** None. **K. Heslin:** None. **C. Page:** None.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

Location: Halls A-C

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Topic: G.05. Anxiety Disorders

Support: PHS grant MH093981 to Rita Valentino

NIH 5T32NS007413-17 to Kimberly Urban

Title: Age and sex dependent effects of repeated social stress on rat prefrontal cortical pyramidal neuron morphology

Authors: *K. R. URBAN[1], E. GENG[2], S. BHATNAGAR[3], R. J. VALENTINO[4]
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Abstract: Chronic stress can lead to psychiatric illness characterized by impairments of executive function, implicating the prefrontal cortex as a target of stress-related pathology. Previous studies have shown that multiple types of chronic stress reduce dendritic branching, length and spines of medial prefrontal cortex (mPFC) pyramidal neurons. However, these studies largely focused on layer 2/3 pyramidal neurons in adult male rats. Whereas these neurons process incoming information, layer 5 is the major output layer. Because the prefrontal cortex develops throughout adolescence, stress during this period may have a greater impact on structure and function than stress occurring during adulthood. Furthermore, females display greater risk of stress-related psychiatric disorders, indicating sex-specific responses to stress. In this study, male and female adolescent (42-48 days old, 4 rats per group) or adult (68-72 days old, 4 rats per group) Sprague-Dawley rats were exposed to repeated social stress as 5 days of resident-intruder stress or control manipulation. Brains were Golgi stained 24 hrs after the final manipulation, cells were visualized on a Nikon Eclipse scope, and Neurolucida was used to trace neurons and analyze dendrites. Stress resulted in layer, age, and sex-specific effects. In layer II/III, stress reduced apical dendritic branching in male and female adolescents (Age*Stress interaction: $F(1,238)=12$, $p=0.0006$) and basal dendritic branching of adult male rats (Age*Sex*Stress interaction: $F(1,238)=6.6$, $p=0.01$; Tukey's post-hoc, $p<0.05$). Notably, in layer V, stress increased apical branching in adult males and decreased it in all other groups

(Age*Sex*Stress interaction: $F(1,257)=7.2$, $p<0.01$; Student's t-test $p<0.05$). Social stress also, increased branching of layer V basal dendrites selectively in adult male rats (Age*Sex*Stress interaction: $F(1,257)=12.4$, $p=0.0005$). These results suggest that repeated social stress particularly during adolescence reduces PFC neuronal complexity, which may result in impairments in executive function and PFC-dependent cognition. That resident-intruder stress had the unique ability to increase mPFC dendritic complexity of adult males implies that this experience is perceived differently by this population and suggests that the experience of fighting for dominance may selectively enhance cognitive processing for this group.
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Poster

701. Behavioral Effects in Preclinical Models of Anxiety

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: G.05. Anxiety Disorders

Support: Research Project Grant A by Institute of Science and Technology Meiji University

Title: Strain differences in learning ability and emotional behavior of Hatano high and low avoidance rats

Authors: *K. KAWAKAMI[1], T. OKAWARA[2], K. MUSYA[2], Y. HORI[2], R. OHTA[3], M. KAWAGUCHI[2]
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Abstract: Inbred strains of Hatano high- (HAA) and low- (LAA) avoidance rats, derived from the Sprague-Dawley strain, were selectively bred based on their respective avoidance performances in the shuttle-box active avoidance task. To clarify the behavioral characteristics of the Hatano rats, male HAA and LAA rats, were subjected to behavioral tests for learning ability (step-through type passive avoidance, social recognition and novel object tests) and for emotionality (elevated plus maze test). As a result, the avoidance performance in the passive task was significantly greater in HAA than LAA rats. In elevated plus maze test, LAA rats showed higher percentage time spent exploring open arms compared to HAA rats. Also, in the social recognition tests HAA spent more time investigating novel animals than familiar animals but LAA showed no differences. In contrast, there was no strain difference between the HAA and LAA rats in the novel object tests. These results suggest that avoidance performance in the Hatano HAA and LAA rats is almost not resulted in cognitive function. Although the HAA rats

showed higher anxiety behavior than LAA rats, avoidance learning and social recognition are known to be associated with emotion. Therefore, Hatano HAA and LAA rats can be useful models which show clear strain differences in learning ability involved with anxiety behavior. Part of this experiment was conducted by a Meiji University Priority Research grant.

Disclosures: K. Kawakami: None. **T. Okawara:** None. **K. Musya:** None. **Y. Hori:** None. **R. Ohta:** None. **M. Kawaguchi:** None.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 701.10/QQ10

Topic: G.05. Anxiety Disorders

Support: NIH Grant NS048602

Title: Unguided identification of mouse behavioral phenotypes

Authors: *J. G. MCCALL[1], C. C. HAMMARSTEN[3], A. A. BORD[3], M. E. SHELTON[3], T. D. SHEAHAN[2], J. P. GOLDEN[2], R. W. GEREAU, III[2]
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Abstract: Preclinical animal studies are critical to advancing basic neuroscience and clinical medicine. However, most animal behavior assays rely on preconceived notions regarding the important observed features of the dataset, rather than unbiased assessment of the fundamental structure of the data. To address this shortcoming, we used persistent homology, a mathematical method for computing important topological data structures, to blindly identify salient features in mouse behavior data. This approach generated a 'diagnostic framework' to assess the behavioral phenotype of individual animals. As a proof-of-principle, we examined the locomotor behavior of more than one hundred mice that had either been stressed or not. In a double-blind fashion, the persistent homological analyses successfully identified two groups of mice. These two mathematically-identified were largely segregated by stress exposure. Using the persistent homological features of these two groups, we were then able to test new animals against this ‘training set’ to blindly determine whether new animals had been stressed. Testing new animals against this ‘training set’ we can blindly predict whether new animals had been stressed and whether commonly used anxiolytics could reverse these unguided classifications. This approach yields greater than 90% accuracy using only the XY position coordinates in an open field. We next asked if the same could be done for pain. Acute models of inflammatory pain do not classify as stressed in this system, while chronic, injury-induced models of neuropathic pain do cause animals to be blindly ‘diagnosed’ as stressed. This distinction may be useful in considering and

modeling psychiatric sequelae following evoked pain, but it will be important to use an analogous persistent homology approach to generate a new 'diagnostic framework' for identifying spontaneous pain in animal models. This mathematical approach is capable of identifying critical features of animal behavioral data that may not otherwise be recognized by human observers. Such an unguided 'diagnostic framework' may be useful in modeling psychiatric disorders and potential therapeutic approaches.

Disclosures: J.G. McCall: None. **C.C. Hammarsten:** None. **A.A. Bord:** None. **M.E. Shelton:** None. **T.D. Sheahan:** None. **J.P. Golden:** None. **R.W. Gereau:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurolux Inc..

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

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Topic: G.05. Anxiety Disorders

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CONACYT grant 243247

VIEP-BUAP 2017

BUAP-CA-288

SLRG is fellowship of SNI-3 to JRE

Title: Analgesic effects of tramadol in male and female rats with an anxious trait

Authors: *C. CORTES[1], J. EGUIBAR[2], S. L. RUGERIO[3], M. MARTINEZ-GOMEZ[4]
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Abstract: A close relationship has been established between anxiety and pain. On the other hand, chronic stress exposure is associated with an increase in pain sensitivity, because produce a greater response to it, known as: stress-induced hyperalgesia. The high- and low- yawning (HY and LY, respectively) are two selectively inbreed lines from Sprague-Dawley (SD) rats. The HY and LY rats differ in the number of grooming bouts in a novel environment or after wetting the fur and in the open-field arena HY rats showed higher ambulation scores and thigmotaxis suggesting a higher anxiety respect to LY. The aim of this study was to analyse the sexual

dimorphism and the analgesic effect of tramadol on HY and LY using the tail-flick latency apparatus. The involvement of opioid receptors in the analgesic mechanism was investigated using adult female and male rats from both lines. All rats were maintained under standard conditions with 12:12 light: dark cycle (lights on 0700). We measured tail-flick latencies in three experimental sessions, at 30, 180 and 360 min after intraperitoneal injection of 10 mg/Kg of tramadol, an opioid drug with high affinity for mu opioid receptors. Each session consisted of three determinations of tail flick latencies after drug administration with 30-second intervals between them. All data are the mean ± error standard of mean. All procedures described were performed followed the NIH guide for the Care and Use of Laboratory Animals. Benemérita Universidad Autónoma de Puebla Animal Care and Use Committee approved all experimental procedures COSCM-SAL17-G. Our results showed that nociceptive response in the female and male rats differ between sublines and SD strain. HY rats had a lower pain threshold respect to LY and SD (ANOVA, $F_{(2,1)} = 22.4$, $P < 0.001$, followed by Tukey test, $P < 0.001$) and was lowest in females than males. Systemic administration of tramadol increased pain threshold in female rats (ANOVA, $F_{(2,1)}=3$, $P<0.05$), but it produced lower effects in all group of rats, being higher in LY and SD rats, and the opposite happen in HY line. In conclusion, pain responses are sexually dimorphic. The analgesic responses were modified by tramadol in female rats but it is not the case in all three groups of male rats.

Disclosures: C. Cortes: None. **J. Eguibar:** None. **S.L. Rugerio:** None. **M. Martinez-Gomez:** None.

Poster

701. Behavioral Effects in Preclinical Models of Anxiety

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Program#/Poster#: 701.12/QQ12

Topic: G.05. Anxiety Disorders

Support: NIH Grant 1R01MH105447-01

Title: Rats bred for high propensity to anxiety- and depression-like behavior display altered mitochondrial markers in limbic brain regions

Authors: *J. P. HUAMAN, C. R. MCCOY, S. M. CLINTON
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Abstract: Affective disorders like major depression and anxiety have been studied extensively, yet the molecular underpinnings of these debilitating illnesses have yet to be completely identified. While dysfunction of monoamine neurotransmission has long been associated with the pathophysiology of affective disorders, other theories posit that disturbances of mitochondrial function and metabolic activity within certain limbic brain regions also plays a role. The present

study uses a rodent model of a depression/anxiety-like phenotype to examine how metabolic differences in the limbic brain may relate to high levels of anxiety and depression-like behavior. Specifically, we use rats bred for low vs. high behavioral response to novelty; low novelty responding (LR) rats exhibit high levels of anxiety- and depression-like behavior compared to high novelty responding (HR) rats. Our previous transcriptome profiling study revealed numerous metabolism-related gene differences in the amygdala and hippocampus of LR vs. HR rats. We also found evidence of metabolic differences in the developing HR/LR brain by examining activity of Cytochrome C Oxidase (COX), one of the enzymes responsible for ATP production and a metabolic activity marker. The current study aims to find if these differences persist in adulthood. We first assessed COX activity in the hippocampus and amygdala of adult male HR/LR rats and found reduced COX activity in the central nucleus of the amygdala of LR versus HR rats. We next analyzed basal oxygen consumption with a Seahorse Biosciences XF24 Flux analyzer. Using freshly dissected hippocampus and amygdala of adult male HR/LR rats, we isolated mitochondria through differential centrifugation and a Ficoll gradient. In ongoing experiments, we expect that oxygen consumption levels will correlate with COX activity in both the amygdala and hippocampus. Therefore, we anticipate that LR rats will have decreased oxygen consumption relative to HRs in the amygdala and hippocampus. Overall, our results add to a growing literature suggesting that perturbations of metabolic and mitochondrial activity in the limbic brain may lead to disparate emotional behavioral phenotypes and affect vulnerability to emotional disorders.

Disclosures: **J.P. Huaman:** None. **C.R. McCoy:** None. **S.M. Clinton:** None.

Poster

702. Developmental Effects of Addictive Drugs

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 702.01/QQ13

Topic: G.08. Drugs of Abuse and Addiction

Title: A sex-specific role of prenatal testosterone in adult alcohol and water drinking in mice

Authors: *C. P. MUELLER[1], I. ZOICAS[1], M. REICHEL[1], C. MUEHLE[1], C. BUETTNER[2], A. B. EKICI[2], B. LENZ[1], J. KORNHUBER[1], S. E. HUBER[1]
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Abstract: Correlational studies in humans suggested organizational testosterone effects during embryonic development as a risk factor for adult alcohol dependence. However, a causal relationship has never been demonstrated. The aim of this study was to investigate the role of dihydrotestosterone (DHT) and flutamide, a synthetic testosterone receptor antagonist, administered during the prenatal period on adult emotional behavior and alcohol consumption in

male and female mice. Here we demonstrate a relationship between prenatal androgen receptor (AR)-activation and adult alcohol as well as water drinking in mice in a sex-specific way. Prenatal flutamide decreased adult alcohol consumption only in males. In contrast, prenatal AR activation by DHT led to an increase in adult alcohol consumption only in females. Virtually opposite effects were observed for adult water drinking. Prenatal flutamide increased adult water consumption only in females and DHT increased water consumption only in males. Prenatal flutamide reduced locomotion and anxiety in adult males, but was ineffective in females. Furthermore, we found that prenatal AR activation controls adult levels of monoaminergic modulatory transmitters in the brain and blood hormone levels in a sex-specific way. A RNA-Seq analysis confirmed a prenatal AR mediated control of adult expression of alcohol drinking-related genes like *Bdnf* and *Per2*. These findings suggest an important organisational role of prenatal AR activation in adult alcohol- as well as water drinking behavior, which is sex-specific.

Disclosures: C.P. Mueller: None. **I. Zoicas:** None. **M. Reichel:** None. **C. Muehle:** None. **C. Buettner:** None. **A.B. Ekici:** None. **B. Lenz:** None. **J. Kornhuber:** None. **S.E. Huber:** None.

Poster

702. Developmental Effects of Addictive Drugs

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 702.02/QQ14

Topic: G.08. Drugs of Abuse and Addiction

Support: NSERC Discovery Grant

Canada Foundation for Innovation

Title: Developmental ethanol exposure and prefrontal layer VI neurons: Near-term effects on neuron structure and function

Authors: *E. L. LOUTH, C. D. SUTTON, L. K. SPATAFORA, C. F. KUPKA, C. D. C. BAILEY
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Abstract: Chronic exposure to ethanol during development can lead to a variety of teratogenic outcomes known in humans as Fetal Alcohol Spectrum Disorders (FASD). Although attention deficits comprise one of the most prevalent neurocognitive impairments associated with FASD, the neural mechanisms underlying this outcome remain unknown. We have shown previously that adult mice exposed to ethanol during development exhibit impaired performance on an attention task, along with dysregulated morphology and physiology of pyramidal neurons in the medial prefrontal cortex (mPFC) layer VI that are critical for normal attention. This current study aims to determine whether these developmental ethanol-induced alterations to mPFC layer VI

neurons are also present early in postnatal life, to gain a better understanding of how and when the adult phenotype emerges. Developing mice were administered binge-like ethanol treatment or air (control) using vapour chambers from gestational days 10 to 18 (term, 19 days) and from postnatal days (P) 4 to 14. Electrophysiological and morphological properties of mPFC layer VI pyramidal neurons were measured at P15 and P25 in male and female mice. Electrophysiological experiments reproduced known effects of age and sex on neuron physiology in control mice. In contrast with previous findings for male mice in adulthood, there were no effects of developmental ethanol treatment on basic electrophysiological properties, or on nicotinic and AMPA receptor function in male mice at P15 or P25. Nicotinic receptor function was increased by developmental ethanol treatment in female mice, suggesting that this alteration to layer VI neuron physiology varies by sex and occurs earlier in females. Reconstruction and morphological analysis of recorded neurons also shows sexually dimorphic effects of developmental ethanol exposure on dendrite morphology and spine density. Together, these results demonstrate sex-specific alterations to mPFC layer VI neuron physiology and morphology in young postnatal mice following developmental ethanol exposure.

Disclosures: E.L. Louth: None. **C.D. Sutton:** None. **L.K. Spatafora:** None. **C.F. Kupka:** None. **C.D.C. Bailey:** None.

Poster

702. Developmental Effects of Addictive Drugs

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH

NIAAA

ABMRF

NARSAD

CTSI

Scot-Gentle foundation

Title: Epigenetic changes associated with motor skill learning elicited by prenatal alcohol exposure

Authors: *M. SHAHID[1], S. ISHII[1], P. LI[1], A. I. SON[1], L. WANG[2], Z. M. N. QUEZADO[2], F. IMAMURA[3], J. LIU[1], Y. I. KAWASAWA[3], M. TORII[1,4,5], K. HASHIMOTO-TORII[1,4,5]

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Abstract: Prenatal environmental challenges such as alcohol or drug exposures increase risks of learning and intellectual disabilities in children. Our previous report showed that the activated Heat Shock signaling is required for protection of the cells in the embryonic mouse cerebral cortex exposed to such prenatal challenges. However, the long term consequences of these survived cells and their contribution to neurobehavioral deficits remain elusive. To address these questions, we developed a novel reporter system, which enables lineage tracing of these cells. By performing single cell RNA sequencing of the reporter positive and negative neurons in the adult mice exposed to alcohol prenatally, we identified epigenetic changes, revealed by differentially expressed genes (DEGs) between the reporter-positive and -negative neurons. These DEGs include the genes whose functions are critically involved in the long-term potentiation of the neurons, suggesting a possibility that the epigenetic changes linked to the prenatal activation of Heat Shock signaling contribute to the neurobehavioral impairments in those mice. Pharmacological treatment for one of the identified epigenetic changes improved motor learning deficits in the mice that were exposed to alcohol prenatally. These results showed that reversal of key epigenetic changes may become a therapeutic approach for those who are exposed to prenatal challenges and show neurobehavior problems.

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Poster

702. Developmental Effects of Addictive Drugs

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 702.04/QQ16

Topic: A.01. Neurogenesis and Gliogenesis

Support: ÁÁ013440

ÁÁ024659

Title: A novel pseudogene-encoded long noncoding RNA mediates fetal alcohol effects

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Abstract: Prenatal alcohol exposure is a leading non-genetic cause of neurodevelopmental disability. Neural stem cells (NSCs) that give rise to most neurons of the adult brain during the first and second trimester are particularly vulnerable. We previously found that ethanol exposure did not result in NSC death, but rather, the loss of NSCs due to premature maturation. This effect was mediated in part by the loss of specific miRNAs in NSCs. Here, we investigate whether ethanol also specifically prevents NSC renewal. We assessed the regulation of the homeobox transcription factor, Oct4/POU5F1, which is important for maintaining stem cell renewal and pluripotency. The Oct4 family includes a number of transcribed pseudogenes that are thought to be long non-protein coding RNAs (lncRNA). We hypothesized that these lncRNAs sequester miRNAs, though they may also have additional functions. We identified Oct4pg9 as one pseudogene-derived lncRNA transcript that was expressed in NSCs at significantly higher levels than the parent Oct4 mRNA transcript. Moreover, Oct4pg9 is transcribed at significantly higher levels in NSCs than differentiating neurons. Oct4pg9 binds Ago2 in both the nucleus and cytoplasm of NSCs, supporting its role as a miRNA sponge. Additionally, preliminary data shows that Oct4pg9 associates with ribosomes suggesting that it may regulate RNA translation or encode novel micro-peptides. Ethanol exposure results in elevated levels of Oct4pg9, whereas Oct4 protein levels are reduced. We studied the effect of ethanol exposure on the expression of Oct4 and Oct4pg9. Oct4 protein level was decreased in NSCs by ethanol exposure, and Oct4pg9 lncRNA was increased. We assessed the effect of elevated Oct4pg9 on stem cell fate markers in NSCs and compared it to the effects of ethanol. Oct4pg9 overexpression resulted in decreased Nestin, but increased GLAST, DCX, NeuN and GFAP transcripts. This effect was mimicked by ethanol exposure. In contrast, siRNA-mediated Oct4pg9 knockdown results in elevated Oct4, REST and Nestin mRNA transcripts and downregulation of DCX mRNA. These data suggest that ethanol-mediated elevation of Oct4pg9 shifts NSCs towards a neuronal/oligodendrocytic fate. Our results suggest that this novel lncRNA member of the Oct4/Pou5f1 family may regulate NSC renewal and mediate some of the teratogenic effects of ethanol.

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Poster

702. Developmental Effects of Addictive Drugs

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIAAA: U01AA019972

Title: Adolescent ethanol exposure induces social anxiety and alters the balance between the oxytocin and vasopressin systems

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Abstract: Adolescent intermittent ethanol exposure (AIE) produces lasting, sex-specific adverse social consequences, with male, but not female, rats exhibiting social anxiety-like alterations (i.e., decreases in social investigation and social preference) as adults. Oxytocin (OXT) and vasopressin (AVP) brain systems play critical, although often opposite, roles in regulating social preference/avoidance, with OXT predominantly increasing approach to and AVP increasing avoidance of social stimuli. Using biochemical and psychopharmacological approaches, the present study tested the hypothesis that social anxiety seen in adult males after AIE is associated with a shift in the balance between the OXT and AVP systems toward AVP. Specifically, we assessed (1) effects of AIE on OXT, vasopressin V1a and V1b receptors (OXTR, V1aR, and V1bR, correspondingly) surface expression in the hypothalamus, and (2) effectiveness of pharmacological activation of the OXT system and blockade of endogenous activity at AVP receptors in reversing AIE-induced social anxiety using a modified social interaction test. Sprague-Dawley rats housed in groups of four littermates were given 4 g/kg ethanol (25%) (AIE) or water (control) intragastrically every 48 hr for a total of 11 exposures from postnatal days (P) 25-45. Behavioral testing and brain tissue collection occurred during early adulthood (P70 - P84). For social testing, subjects were injected intraperitoneally (i.p.) with vehicle, or a selective OXTR agonist WAY 267,424 (0.0, 2.5, or 5.0 mg/kg), V1aR antagonist SR 49059 (0.0, 1.0, 3.0, or 9.0 mg/kg), or V1bR antagonist SSR 149415 (0.0, 5.0, 10.0, or 20.0 mg/kg). Results indicated that AIE decreased OXTR, but increased V1bR neuronal surface expression relative to water-exposed controls. V1aR was not impacted. Behavioral testing again revealed decreases in social investigation and social preference in AIE males, confirming our prior findings of lasting social anxiety induced by AIE in males. Importantly, this AIE-induced social anxiety was reversed by the selective OXTR agonist and V1bR antagonist, whereas the V1aR antagonist did not rescue normal social behavior. Taken together, these results support the hypothesis that social anxiety induced by AIE is associated with an OXT/AVP imbalance, providing support for a novel pharmacotherapeutic approach to reverse the lasting consequences associated with adolescent binge-level ethanol exposure.

Disclosures: C. Dannenhoffer: None. **D.F. Werner:** None. **E.I. Varlinskaya:** None. **L.P. Spear:** None.

Poster

702. Developmental Effects of Addictive Drugs

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 702.06/QQ18

Topic: G.08. Drugs of Abuse and Addiction

Support: ES022831

EPA 83543701

Title: Gestational exposure to low concentrations of tobacco smoke components, nicotine and benzo-a-pyrene, diminishes normal sex-differences in behavior in rats

Authors: *A. B. HAWKEY, S. JUNAID, L. YAO, Z. SPIERA, M. CAULEY, C. WELLS, H. WHITE, E. LEVIN
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Abstract: Tobacco smoke is a complex mixture containing thousands of different chemicals. Tobacco smoking during pregnancy has been associated with impaired neurobehavioral development in their children. In our earlier studies, tobacco smoke extract has been shown to cause persisting hyperactivity and cognitive impairment in rats. Nicotine, the primary psychoactive component in tobacco, can cause cognitive impairment in rats, although there are a variety of other bioactive compounds in tobacco smoke which may also play a role. Prominent among these are polyaromatic hydrocarbons (PAHs). The prototypic PAH is benzo-a-pyrene (BaP), which has also been shown to cause neurobehavioral impairment in rats. The current study was conducted to characterize the individual and combined neurotoxicity of nicotine and BaP during gestational development, including their impacts on behavior in adolescence. Female Sprague-Dawley rats were implanted with osmotic minipumps delivering nicotine (2 mg/kg/day), BaP (0.03 mg/kg/day), both or neither. The male and female offspring were assessed in a behavioral test battery including tests of locomotor activity, as well as emotional and cognitive function. Gestational BaP exposure caused locomotor hyperactivity in male offspring but not females. This effect eliminated the normal sex difference in activity, with BaP treated males rising to control female levels. Additionally, gestational exposure to either nicotine or BaP enhanced the suppression of feeding in a novel environment among male subjects, but not females. This effect eliminated normal sex differences in this outcome. Gestational exposure of rats to low-doses of BaP and nicotine, two constituents of tobacco smoke, caused lasting neurobehavioral effects particularly in male offspring, by diminishing normal differences between males and females. This work was supported by the Duke University Children's Environmental Health Center funded by the National Institutes of Health (ES022831) and by the U.S. Environmental Protection Agency (83543701).

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Poster

702. Developmental Effects of Addictive Drugs

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Topic: G.08. Drugs of Abuse and Addiction

Support: Research supported by National Institutes of Health (R21 DA040228)

Title: Developmental nicotine exposure and Chrna5 D397N genotype impact pre-pulse inhibition across multiple generations: A model for differential outcomes in schizophrenia?

Authors: *H. C. O'NEILL, J. A. STITZEL
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Abstract: The nonsynonymous variant (rs16969968) in the α5 nicotinic receptor subunit gene (CHRNA5), known to be a strong genetic risk factor for nicotine dependence, has recently been linked to schizophrenia. Studies have shown the adult mouse homozygous for the nicotine dependence risk allele (N397, as opposed to the wild-type [WT] D397) suffers from hypofunctionality in the prefrontal cortical region as well as impaired prepulse inhibition (PPI) as compared to D397 WT mice. We have investigated PPI in adolescent mice and found it is impaired by 45 days of age in the N397 mouse. Building on these studies, we have evaluated both first generation offspring (F1) of D397N mice directly exposed to nicotine (100 μg/ml in 0.2% saccharin) from conception through weaning (dev nic) as well as mice who are the second generation (F2) offspring (themselves not exposed directly to nicotine except germline) of F1 mothers exposed to nicotine. Both sexes were evaluated. Following developmental nicotine exposure in the F1 offspring, the D397 dev nic mouse has impaired PPI as compared to their same-genotype vehicle controls; N397 dev nic mice show improved PPI. Interestingly, we see this phenomenon persist in F2 mice, with D397 mice having similar impairments in PPI as F1 dev nic mice. N397 F2 mice are similar to F1 dev nic mice with improvement in PPI as compared to their genotype vehicle controls. This suggests epigenetic modifications of DNA are persisting at least into the F2 generation following developmental nicotine exposure. Early evaluation of global methylation changes indicates significant changes in both the prefrontal cortex and the striatum of mice in F1 and F2 generations respectively. Combined, these data indicate the significant impact of the interaction of the rs16969968 risk variant with developmental nicotine exposure over multiple generations. Further evaluation of epigenetic alterations in pathways relevant to these behaviors will allow a better understanding of how these interactions have the potential to impact multiple generations.

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Poster

702. Developmental Effects of Addictive Drugs

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Topic: G.08. Drugs of Abuse and Addiction

Support: Tobacco-Related Disease Research Program Project Grant 22RT-0103

National Alliance for Research on Schizophrenia and Depression Young Investigator Grant 21517

Undergraduate Research Opportunities Program (UROP), University of California, Irvine

Title: Age-dependent effects of low-dose nicotine pre-exposure on adolescent and adult alcohol and cocaine preference

Authors: *A. M. CARDENAS[1], J. A. TIRTORAHARDJO[2], S. W. LIU[3], Y. YIN[3], Y. BAI[3], S. LOTFIPOUR[2]
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Abstract: In human and rodent studies, adolescent nicotine exposure enhances the use of other drugs of abuse (i.e. the 'gateway hypothesis'). To test the hypothesis in our laboratory for alcohol and cocaine, we pre-exposed adolescent and adult male C57BL/6J mice to low-dose nicotine (equivalent to 1-2 cigarettes) and subsequently assessed drug self-administration or preference. For alcohol, we pre-exposed adolescent and adult male mice to a 7-day treatment regimen of nicotine (2x 0.5 mg/kg/s.c./day) or vehicle and assessed drug intake and preference using the Drinking in the Dark and two-bottle choice behavioral paradigms, respectively. For cocaine, we pre-exposed adolescent and adult male mice to a 4-day treatment regimen of nicotine (2x 0.5 mg/kg/s.c./day) or vehicle and assessed drug reward using the unbiased conditioned place preference behavioral paradigm. For alcohol, after a 7-day washout, late adolescent mice consume significantly more fluid than adults, independent of nicotine pretreatment or fluid self-administered. On alcohol preference test, all groups of animals illustrate preference, except for nicotine pre-exposed alcohol drinking adults. For cocaine preference, after a 7-day washout, nicotine pre-exposure during adolescence, but not adulthood, enhances cocaine reward. The effects are not confounded by differences in blood alcohol levels or cocaine-induced locomotion. Taken together, results provide supportive evidence for age-dependent effects of nicotine pre-exposure on alcohol and cocaine preference in mice.

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Poster

702. Developmental Effects of Addictive Drugs

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Program#/Poster#: 702.09/QQ21

Topic: G.08. Drugs of Abuse and Addiction

Title: Prenatal nicotine alters membrane and synaptic responses of laterodorsal tegmental (LDT) neurons to postnatal alcohol exposure

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Abstract: Using drugs of abuse while pregnant has tremendous negative consequences for the developing fetus. Chief among the negative legacies bestowed to the exposed individual is an enhanced proclivity to addict to drugs later in life. The heightened likelihood that a person exposed to addictive drugs *in utero* will addict suggests that early exposure to drugs changes the developing brain in such a way that biases it towards addiction, presumably via alterations in the developmental trajectory of neurons important in development of addiction, which can lead to later life changes in responsiveness to stimuli. However, it is not well understood what changes are induced by prenatal exposures to nicotine in drug addiction-related areas, such as the LDT. Via projections sent to the ventral tegmental area (VTA), the LDT gates the behaviorally relevant firing pattern signaling stimuli saliency in mesoaccumbal circuits. Therefore, we investigated whether prenatal exposure to nicotine alters the responsiveness of neurons in the LDT to another addictive drug, alcohol. Accordingly, using whole-cell, voltage clamp recordings, we examined miniature postsynaptic inhibitory and excitatory currents (mIPSCs, mEPSCs) and membrane currents induced by alcohol (40mM) in neurons of the LDT from NIMH mice (PN9 to PN20) prenatally exposed to nicotine (PNE; 300µg/ml of nicotine with 2% saccharine) and compared those to control animals (SAC; 2% saccharine). We found that alcohol induced an outward current in the majority of LDT cells from the SAC animal, which was not an effect seen in LDT PNE neurons. Although alcohol tended to increase the frequency of mIPSCs in the SAC and decrease the frequency in the PNE, this differential effect was not significant. Further, while alcohol enhanced the amplitude of mIPSCs in PNE cells, and tended to decrease it in SAC neurons, these effects were not consistent enough to achieve significance between the two animal models. In the SAC animal, alcohol failed to have a significant effect on the frequency or amplitude of mEPSCs. Similarly, the amplitude of mEPSCs was not altered in the PNE by alcohol. However, in a stark contrast to findings in the SAC animal, the frequency of

mEPSCs was decreased by alcohol in all LDT PNE cells. In summary, PNE was associated with alterations in membrane and synaptic responses to postnatal exposures to alcohol. The differences in alcohol responses in the PNE could lead to differential output from the LDT to the VTA, and alterations in this output could play a role in biasing coding of relevant stimuli, which could participate in the enhanced proclivity to addict in those exposed during gestation to nicotine.

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Poster

702. Developmental Effects of Addictive Drugs

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Topic: G.08. Drugs of Abuse and Addiction

Support: GM083883

DA033877

Title: Effects of ketamine on the unconditioned and conditioned locomotor activity of male and female preadolescent and adolescent rats

Authors: *A. E. MORAN, T. J. BAUM, M. J. APODACA, V. REAL, V. GOMEZ, S. A. MCDOUGALL
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Abstract: Ketamine is a dissociative anesthetic used to induce anesthesia in children and adults, a quick-acting treatment for major depression, and an illicit drug commonly used at rave parties. Although ketamine is a non-competitive NMDA receptor antagonist, it may produce some of its anesthetic, anti-depressive, and psychotropic effects via actions involving the DA system. The ability of ketamine to enhance DA neurotransmission has been attributed to the modulation of afferent inhibitory interneurons in DA target areas, while others suggest that ketamine acts as an indirect DA agonist. The purpose of this project was to examine the effects of ketamine on the unconditioned and conditioned locomotor activity of male and female rats during early ontogeny. Because of the potential translational relevance to young humans, we compared rats from the preadolescent and adolescent periods. It was originally hypothesized that adolescent female rats would exhibit more robust unconditioned and conditioned locomotor activity than male rats. Preadolescent rats were also hypothesized to show ketamine-induced unconditioned and conditioned activity, however no sex differences were predicted in this prepubertal age group. To assess unlearned locomotor activity, rats were injected with saline or ketamine (5-40 mg/kg) and distance traveled was measured on PD 21-25 or PD 41-45. To assess conditioned activity, rats

were injected with saline or ketamine (10 or 40 mg/kg) in either a novel test chamber or the home cage on PD 21-24 or PD 41-44. One day later, rats were injected with saline and conditioned activity was assessed. Among adolescent rats, ketamine produced a dose-dependent increase in locomotor activity that was significantly stronger in females than males. Preadolescent rats also exhibited a dose-dependent increase in ketamine-induced locomotor activity, but the drug effects did not differ according to sex. In both age groups, repeated ketamine treatment neither caused a day-dependent increase in locomotor activity (behavioral sensitization) nor produced conditioned activity. The activity-enhancing effects of ketamine are consistent with the actions of an indirect DA agonist, while the inability of ketamine to induce conditioned activity is unlike what is observed after repeated cocaine or amphetamine treatment. This dichotomy could be due to ketamine's ability to both enhance DA neurotransmission and antagonize NMDA receptors. Additional research will be necessary to parse out the relative contributions of DA and NMDA system functioning when assessing the behavioral effects of ketamine during early ontogeny.

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Poster

702. Developmental Effects of Addictive Drugs

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH GM-64783

NIH GM-08807

Title: Repeated administration of ketamine and phencyclidine in adolescence has effects that last into adulthood

Authors: *T. ZAFAR[1], A. ROCHA[2], K. A. TRUJILLO[1]
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Abstract: Dissociative drugs, a class that includes ketamine, phencyclidine and related drugs, are popularly abused, especially by teens and young adults in club and rave settings. According to users, at low doses these drugs produce stimulation and excitation, feelings of euphoria, lucid intoxication, and increased empathy. Since research has concentrated on adult drug abuse little is known of the effects of these drugs in adolescents, and potential differences between adolescents and adults. Tolerance and sensitization are types of neuroplasticity that contribute to drug abuse and addiction. Whereas tolerance is a decrease in an effect of a drug after repeated use,

sensitization is an increase in an effect of a drug after repeated administration. The present study examined ultrasonic vocalizations (USVs) in adolescent and adult Sprague Dawley rats after repeated exposure to PCP and KET. USVs reflect the affective state of the animal and are increased by drugs of abuse, most notably the psychomotor stimulants. We hypothesized that PCP and KET would induce a successive increase in ultrasonic vocalizations across days of treatment, reflective of sensitization, and that adolescent rats would show greater sensitization than adults. Animals received saline, KET (10 mg/kg s.c) or PCP (3 mg/kg s.c), once daily for seven days and USVs were assessed each day. On day 1 of treatment, both ketamine and PCP induced short-lived increases in USVs that were greater in adolescents than adults. Surprisingly, sensitization was seen following repeated administration of KET in adolescents, but tolerance was apparent following repeated administration of PCP - these changes were seen in adolescents, but not adults. Thus, while repeat administration of KET leads to behavioral sensitization in adolescents, repeat administration to PCP leads to tolerance. Interestingly, these changes persisted when adolescents were tested again as adults. Further research will help to determine the factors involved in KET sensitization and PCP tolerance. The results may lead to better prevention and treatment for KET and PCP abuse and addiction in teenagers.

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Poster

702. Developmental Effects of Addictive Drugs

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant K23MH079498

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Title: NMDA receptor blockade has differential effects on the synaptic proteome in juvenile versus adult mice

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Abstract: Previously we observed that chronic ketamine decreased N-methyl-D-aspartame (NMDA) receptor signaling in adult mice but increased it in juveniles. In addition, we found that

NMDA receptor signaling changes persisted following cessation of treatment at least for 2 weeks in juvenile animals. Such differential effects of NMDA receptor blockade between juveniles and adults are of interest from the perspective of schizophrenia pathophysiology as well as increasing prevalence of ketamine abuse among adolescents. In this study we examined the proteome of synaptic membrane fractions in juvenile and adult mice at 24 hours and two weeks after cessation of a 2 week ketamine treatment. Ketamine (20mg/kg) was administered to adult (10 week) and juvenile (4 week) C3H male mice daily for 2 weeks. Mice were sacrificed after either 24 hours or a two week washout period. Crude synaptic membrane fractions were isolated by centrifugation of the post nuclear extracts of homogenized mouse cortical tissues. Ten µg of synaptic membrane extracts were mixed with [13C6]lysine-labeled internal standards. Samples were trypsin-digested, and processed for LC-SRM/MS on a triple quadrupole mass spectrometer for 200+ synaptic proteins. Peak areas for “light” endogenous peptides and “heavy” standard peptides were calculated, and ratios (l/h) between the two were used as dependent variables. Repetitive ketamine injection started in the juvenile period compared to adulthood (daily injection for 14 days followed by 24 hrs drug washout) led to alterations in more than 60 proteins that differed between the groups including SRC, GluN2B and GluR3 along with multiple mitochondrial proteins (p=0.03, Wilcoxin Rank Sum; multiple comparisons were accounted for using the FDR). Some protein alterations persisted two weeks later in animals exposed to NMDA receptor blockade during the juvenile period. These results point to interesting differences in the effects of the onset of NMDA receptor hypofunction in the juvenile period compared to that in the adult period.

Disclosures: **K. Borgmann-Winter:** A. Employment/Salary (full or part-time):; University of Pennsylvania, Children's Hospital of Philadelphia. **A. Banerjee:** A. Employment/Salary (full or part-time):; University of Pennsylvania. **J. Johnson:** None. **N.M. Bowman:** None. **W. Bilker:** A. Employment/Salary (full or part-time):; University of Pennsylvania. **S.J. Siegel:** A. Employment/Salary (full or part-time):; University of Southern California. **C. Hahn:** A. Employment/Salary (full or part-time):; University of Pennsylvania.

Poster

702. Developmental Effects of Addictive Drugs

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA035251

UC Irvine ICAN EP11510

Title: Effects of adolescent cannabinoid exposure on conditioned and unconditioned natural reward seeking in adult rats

Authors: *C. RUIZ[1], M. HUERTA[2], H. SCHOCH[3], R. R. CAMPBELL[4], S. V. MAHLER[5]
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Abstract: Cannabis use is becoming increasingly widespread in the general pubic and especially among adolescents. Eight states and the District of Columbia have legalized it for recreational use and twenty-eight states have legalized it for medicinal use. As more states consider recreational legalization, there will be an increase in adolescent usage during a critical time of neurodevelopment. The brain's own endocannabinoid signaling, especially anandamide (AEA) and 2-arachidonoylglycerol (2-AG), is critically involved in adolescent neurodevelopment, and one possibility is that exogenous cannabinoid exposure during adolescence disrupts ECB-dependent development of reward-related neural circuits. Studies have already shown adolescent cannabinoid exposure (ACE) leads cognitive and memory impairments, as well as to increased heroin seeking (Ellgren 2007), and decreased social reward (Wei 2016). Here we examine effects of ACE on conditioned and unconditioned reward seeking in male long evans rats. Rats were delivered at post-natal day (PD) 21-23 and on PD30 started daily 1.2mg/kg IP injections of WIN55,212-2 (CB1 agonist) or vehicle for 14 consecutive days. The fourteen-day WIN exposure was succeeded by a fourteen-day washout period with no drug exposure. Following the washout period, the animal completed a Pavlovian conditioned approach task (sign/goal tracking) with a palatable food reward. This task examines individual differences of targeting motivation and rats are identified as sign trackers (preference for predictive lever) or goal trackers (food cup preference). ACE rats showed altered sign and goal tracking as compared to the control group, with more ACE rats showing unusual approach to both sign and goal cues. Next, we examined ACE effects on unconditioned food and novelty reward-related behaviors. Rats were tested for free intake of familiar and novel palatable foods, homeostatic regulation of intake by acute hunger or satiety, locomotor response to novelty, and novel context preference. We observed increased binge-like intake, altered modulation of intake after hunger, and altered responses to novelty. Finally, we examined ECB responses to acute food restriction in several brain regions including nucleus accumbens, medial prefrontal cortex, and cerebellum. In sum, we observe in ACE rats a robust phenotype of increased natural reward seeking, altered responses to reward cues and novelty, and altered ECB system reactivity, potentially indicating an addiction-prone phenotype after adolescent cannabinoid use.

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Poster

702. Developmental Effects of Addictive Drugs

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Topic: G.08. Drugs of Abuse and Addiction

Support: USPHS grant P50 MH103222

Title: Gestational cannabinoid exposure influences extracellular kynurenic acid and glutamate levels in the medial prefrontal cortex of adolescent offspring

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Abstract: Cannabis is the illicit drug most commonly abused by pregnant women. The main psychoactive component of marijuana, delta^9-tetrahydrocannabinol (Δ^9-THC), can reach the fetus through the placenta and the blood-brain barrier. Several longitudinal studies of children and adolescents prenatally exposed to marijuana reported a significant impairment of higher cognitive functions (Smith et al., 2006; El Marroun et al., 2011; Huizink, 2013), as well as a link to psychiatric disorders (Jutras-Aswad et al., 2009; Mathews et al., 2014). Preclinical studies indicate that prenatal exposure to cannabinoids induces cognitive deficits in rat offspring (Ferraro et al., 2009). Moreover, these impairments are associated with alterations of aminoacidergic neurotransmission in the hippocampus and the prefrontal cortex (PFC) (Mereu et al., 2003; Antonelli et al., 2005). In particular, some of the deleterious effects on cognitive functions resemble those observed in adult rats, which had been prenatally exposed to the tryptophan metabolite (L-) kynurenine, the direct bioprecursor of the neuroactive compound kynurenic acid (KYNA) (Pocivavsek et al., 2014). We therefore investigated whether alterations in KYNA levels in the rat brain might play a role in the short- and long-term consequences of prenatal cannabinoid exposure. Pregnant Wistar rats were treated daily with Δ^9-THC [5 mg/kg or vehicle (sesame oil) by oral gavage] from gestational day (GD) 5 through GD 20. Three vehicle-treated and five Δ^9-THC-treated dams were euthanized at GD 20, and the levels of kynurenine and KYNA were determined in maternal and fetal plasma and brain. The remaining dams (n=4 per group) gave birth, and one adolescent [postnatal day (PD) 35-45] male rat per litter was used to determine the extracellular levels of KYNA and glutamate by *in vivo* microdialysis in the medial PFC (mPFC).
No changes were found in kynurenine and KYNA levels in the fetal and maternal plasma or in the fetal and maternal brain. However, extracellular basal KYNA levels in the mPFC were significantly higher in prenatally Δ^9-THC-exposed adolescent rats ($p<0.01$) compared to the vehicle group. In addition, following gestational Δ^9-THC treatment, adolescent rats had significantly lower extracellular glutamate levels than the vehicle group ($p<0.05$). The present data demonstrate that prenatal cannabinoid exposure leads to long-term alterations of KYNA and glutamate levels in the mPFC in adolescence. As an increase in KYNA levels has been associated with cognitive dysfunction and psychiatric disorders, the possibility that this mechanism could underlie the detrimental effects of prenatal marijuana exposure is hypothesized.

Disclosures: **S. Beggiato:** None. **L. Ferraro:** None. **R. Schwarcz:** None.

Poster

702. Developmental Effects of Addictive Drugs

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 702.15/RR5

Topic: G.08. Drugs of Abuse and Addiction

Support: R01 DA033646

K12 GM081259

Title: Neurobehavioral effects of early opioid exposure in mice: Influence of the Oprm1 A112G single nucleotide polymorphism

Authors: *S. A. ROBINSON[1], A. D. JONES[1], M. E. EHRLICH[2], J. A. BLENDY[1]
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Abstract: Infants exposed to opioids in utero are at high risk of developing Neonatal Abstinence Syndrome (NAS), a combination of somatic withdrawal symptoms including high pitched crying, irritability, gastrointestinal distress, and in some cases seizures. Despite being one of the leading causes of neonatal hospital admissions in the U.S., the factors impacting NAS severity are unknown. Furthermore, how this experience impacts behavior later in life has not been well documented. A potential genetic influence of NAS outcome may be a single nucleotide polymorphism (SNP) in the opioid receptor gene (*OPRM1*), which has recently been shown to be associated with shorter length of stay in the hospital for infants with this SNP (Wachman et al., 2015). Using our mouse line possessing the equivalent nucleotide/amino acid substitution in the *OPRM1* gene (A112G), we sought to determine if this SNP modulates the short and/or long term behavioral effects of neonatal opioid exposure in mice. Newborn pups harboring either the A/A or G/G alleles were injected with morphine (10mg/kg) from postnatal day (PND) 1-14 (equivalent to the third trimester of human gestation) and observed for emergence of developmental milestones and withdrawal symptoms. We observed delays in reaching important developmental milestones, such as eye opening, forelimb grasping and ambulations in an open field, with morphine-exposed mice taking longer to reach criteria and trends toward a genotype x morphine interaction. To determine if neonatal morphine exposure and withdrawal produces long lasting effects on behavior, mice exposed to morphine from PND 1-14 were assessed on anxiety-like behavior and drug sensitivity in adulthood. Morphine treated animals showed increased anxiety-like behavior, as measured by reduced time spent in the open arms of the elevated zero maze. Sensitivity to repeated morphine administration assayed through locomotor response showed that morphine exposed animals exhibit significantly blunted locomotor sensitization to repeated morphine. The further development of a mouse model of NAS will allow for more in

depth investigation into the influence of genetic variability as well as provide insights into the underlying neurobiology of this syndrome.

Disclosures: S.A. Robinson: None. **A.D. Jones:** None. **M.E. Ehrlich:** None. **J.A. Blendy:** None.

Poster

702. Developmental Effects of Addictive Drugs

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Topic: A.07. Developmental Disorders

Support: NIH Grant DA025674

NIH Grant T35 OD010963

Title: Prenatal oxycodone self-administration and postnatal outcomes

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Abstract: The levels of prescription opioid use and abuse are at historic levels in the U.S. In addition to increased rates of heroin addiction and opioid-related deaths, this increased exposure to opioids has also resulted in a dramatic rise in the number of babies born to opioid using mothers, many of whom display neonatal abstinence syndromes (NAS). Our understanding of factors that can exacerbate or ameliorate NAS in opioid using women is limited. The use of preclinical models to examine the relationship between specific drug regimens and offspring outcome, including severity of NAS could provide valuable information. The present set of studies utilizes a model of both short and long access oxycodone self-administration in rats which begins prior to conception and continues throughout pregnancy. Outcomes examined include drug-induced alterations in ultrasonic vocalizations, deficits in maternal care, and differences in neural expression of both mu-opioid receptor (MOR) and methyl CpG binding protein 2 (MeCP2) during the early postnatal period.

Disclosures: E.M. Byrnes: None. **A. Toorie:** None. **M. LaPointe:** None. **F.M. Vassoler:** None.

Poster

702. Developmental Effects of Addictive Drugs

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 702.17/RR7

Topic: A.02. Postnatal Neurogenesis

Title: Modeling opioid-mediated neonatal abstinence syndrome (NAS) to improve our understanding of challenges in neurodevelopment

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Abstract: Opioid dependence is at epidemic levels in the USA, it is estimated that over 2.1 million people are suffering from substance use disorders related to prescription opioid pain relievers. Opioid exposure in pregnancy has led to the increase in neonatal abstinence syndrome (NAS). In the US, NAS has increased 5-fold in the last 10 years and was the single greatest reason for neonatal hospital admissions in 2015. Neonates chronically exposed to opioids and thus activation of opioid receptors while in-utero, will experience symptoms of NAS with the abrupt discontinuation of these mechanisms after birth. This leads to increased activation of intracellular signaling, ionic imbalances and increased neurotransmitter activity. Presentation of NAS symptoms are suggestive of such imbalances and are subsequently managed through medicinal opioid therapies to first achieve homeostasis and then to slowly wean the infant off the opioid substance. Currently, the neuropathology behind opioid-mediated NAS is unknown and therefore, warrants further research to improve our understanding of the effects of opioid withdrawal in neonates - this could positively impact clinical outcomes (short and long-term) of infants born with NAS. Data from adult animal models have greatly contributed to our understanding and treatment of opioid tolerance, addiction and withdrawal, however, only a limited number of studies have been conducted to understand the same in neonates. Data from these studies has led to us to conclude that processes are different between adults and neonates, and that neonatal models of opioid withdrawal are vital to understand and develop effective treatment regimens for NAS. Previous models of opioid withdrawal have included large (i.e. sheep and pigs) and small (i.e. guinea pigs, rats and mice) animals using either the spontaneous or precipitated opioid withdrawal paradigm. However, challenges exist with all animal models and in small mammal models brain development at birth differs from that in human neonates. However, using a unique rodent species, the spiny mouse (A. cahirinus) we have developed a spontaneous opioid withdrawal model. With an extended gestational period, A. cahirinus may be an ideal animal model to study NAS. By studying changes in behavior and analyzing brain tissue obtained from aged A. cahirinus born with opioid-induced NAS we hope to determine gender differences that may be used to improve clinical outcomes.

Disclosures: **S. Stevens:** None. **A. Siefert:** None. **S. Mohan:** None.

Poster

703. Amphetamines: Neural Mechanisms of Addiction

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 703.01/RR8

Topic: G.08. Drugs of Abuse and Addiction

Title: Social-based voluntary abstinence prevents the emergence of incubation of drug craving

Authors: *M. VENNIRO, M. ZHANG, D. CAPRIOLI, Y. SHAHAM
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Abstract: Background: We recently developed a rat model of incubation of drug craving after voluntary abstinence achieved by providing rats with a mutually exclusive choice between methamphetamine and palatable food for several weeks. Here we determined whether this incubation phenomenon would occur after a period of voluntary abstinence where the alternative reward is access to a social peer. Methods: We first trained rats to lever-press for either access to a social peer (60-s, 2-h/day, 6 days) or palatable food (5 pellets) and then methamphetamine (0.1 mg/kg/infusion, 6-h/day, 12 days). We then assessed relapse to drug seeking after 1 and 15 abstinence days. Between tests, different groups of rats underwent either social-based voluntary abstinence (15 trials/day), food-based voluntary abstinence (15 trials/day), or homecage forced abstinence. Results: As in our previous studies, non-reinforced responding on the methamphetamine-associated lever in the relapse tests was higher after 15 days of food-choice voluntary abstinence or forced abstinence (incubation of methamphetamine craving). More importantly, rats demonstrated a strong preference for the social peer over methamphetamine (social-based voluntary abstinence). Additionally, prior exposure to social-based voluntary abstinence prevented the emergence of incubation of methamphetamine craving (lever-presses during the relapse test were similar on test days 1 and 15). Conclusions: Results show that exposure to social -based voluntary abstinence prevented the emergence of incubation of drug craving and demonstrate the critical role of social factors in drug relapse, as assessed in animal models. We are currently exploring brain mechanisms underlying the inhibitory effect of social-based voluntary abstinence on incubation of drug craving.

Disclosures: **M. Venniro:** None. **M. Zhang:** None. **D. Caprioli:** None. **Y. Shaham:** None.

Poster

703. Amphetamines: Neural Mechanisms of Addiction

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Support: NSF Graduate Research Fellowship DGE 1058262

NIH R01 DA020725

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Research Grant from Brown Institute for Brain Science

Title: Influence of serotonin transporter SLC6A4 genotype on interaction between stimulant effects and risk-taking in the orbitofrontal cortex

Authors: *A. Z. NITENSON[1], J. E. MCGEARY[2], T. L. WHITE[1]
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Abstract: Serotonin is believed to be heavily involved in risk-taking and assessment, and different serotonin levels in the brain may influence drug response and vulnerability to substance abuse. Brain regions along the serotonergic pathways, including the orbitofrontal cortex (OFC), have been shown to be involved in these mechanisms. The serotonin transporter protein 5-HTT (SERT) is a target site for amphetamines, blocking reuptake and thus increasing synaptic levels of serotonin. In humans, this protein is encoded by the *SLC6A4* gene. The current study investigated the possible influence of a common polymorphism of this gene, 5-HTTLPR, on the interaction between amphetamine effects and the brain's response during risk-taking as measured by fMRI. The within-subject, repeated-measures protocol investigated effects in 52 healthy participants (26M/26F), of whom a final sample of 37 participants (18M/19F) provided genotype information for 5-HTTLPR. Participants underwent two fMRI scan sessions, during which they performed a gambling task with three "Stakes" values (Low, Medium, High). Stakes corresponded to the amount of real-world money that can be earned per trial. Participants consumed a capsule containing either placebo (PLC) or 20-mg *d*-amphetamine (AMP) 90 minutes prior to scanning. Physiological (heart rate, blood pressure) and subjective effects of the capsule were collected over the course of each session. Repeated-measures ANOVAs revealed a significant Drug x Stakes interaction in the left OFC ($F=4.86$, $p=.014$). In this region AMP disrupted the decrease in BOLD activity in response to increased stakes observed in the PLC condition. Our Drug x Stakes x 5-HTTLPR Genotype analysis revealed that this pattern was altered in participants as a function of allelic load. Homozygotes for the high expressing allele showed increased PLC over AMP BOLD activity in the low stakes condition, and those with two

low expressing alleles showed increased AMP over PLC BOLD activity in the high stakes condition. The interaction was significant when using both the biallelic (F=3.41, p=.019) and triallelic (F=4.03, p=.009) genotyping approaches. Furthermore, participants who demonstrated a greater drug response in the left OFC under the high stakes condition reported a greater subjective response to AMP effects (r=.43, p=.003), and were more likely to possess one or more hypofunctional 5-HTTLPR alleles (t=2.37, p=.024). These findings provide insight about the causes of heterogeneous response to stimulants in humans, and suggest a gene/behavior/brain network that underlies susceptibility to drug effects and use.

Disclosures: A.Z. Nitenson: None. **J.E. McGeary:** None. **T.L. White:** None.

Poster

703. Amphetamines: Neural Mechanisms of Addiction

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA032701

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Title: Interactions between methamphetamine and cocaine on dopamine neuron synaptic currents following self-administration experience

Authors: *A. M. HAGER[1], S. DOMINGUEZ-LOPEZ[2], M. J. BECKSTEAD[3]
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Abstract: Dopaminergic neurons are key mediators of substance abuse and addiction-related behaviors. In the midbrain, somatodendritic dopamine release activates inhibitory postsynaptic currents through D2 autoreceptors (D2-IPSCs) coupled to G protein potassium (GIRK) channels on dopamine neurons. The highly addictive psychostimulants cocaine and methamphetamine, alter the mesolimbic dopamine pathway and somatodendritic dopamine neurotransmission. Cross-sensitization between cocaine and methamphetamine has been shown in self-administration behavioral paradigms, however few studies have examined the cellular mechanisms underlying cross-sensitization. In this study we examined the effects of methamphetamine self-administration in mice and alterations in dopamine neurotransmission. Adult mice were trained to nose-poke under a fixed ratio 3 schedule for intravenous infusions of methamphetamine (0.1 mg/kg/infusion) in daily 2 h sessions for 7 to 12 days. Their average intake of methamphetamine was 2.8 mg/kg/day. Whole-cell patch clamp electrophysiology was performed 24 hours following methamphetamine intake. Horizontal brain slices containing

substantia nigra and ventral tegmental area dopamine neurons were taken to examine alterations in D2-IPSCs in response to bath perfusion of various concentrations of methamphetamine or cocaine (100nM-10μM). While methamphetamine self-administration resulted in a downward shift in the methamphetamine concentration-response curve of D2-IPSCs compared to drug-naïve controls, this was not seen in response to bath application of cocaine. Both psychostimulants' mechanism of action involves the dopamine transporter and other cellular adaptations are being investigated such as calcium-dependent mechanisms. These results indicate that doses of methamphetamine sufficient to produce strong behavioral responding are not necessarily high enough to evoke alterations in D2-IPSCs in response to cocaine in midbrain dopamine neurons. A calcium-dependent decrease in dopamine inhibitory neurotransmission in response to methamphetamine but not to cocaine indicates that there is little adaptation in dopamine transporter function following methamphetamine self-administration.

Disclosures: **A.M. Hager:** None. **S. Dominguez-Lopez:** None. **M.J. Beckstead:** None.

Poster

703. Amphetamines: Neural Mechanisms of Addiction

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Bror Gadelius Minnesfond

Fredrik och Ingrid Thurings stiftelse

Fredrik och Ingrid Thurings stiftelse

Title: Spatiotemporal suppression of striatal excitability elicited by amphetamine in Wistar rat

Authors: *A. LOTFI, O. LAGSTRÖM, B. SÖDERPALM, M. ERICSON, L. ADERMARK
Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Amphetamine addiction is a chronic brain disorder, characterized by diminished ability to control drug seeking and a high tendency to relapse. While rewarding effects of amphetamine has been linked to dopaminergic neurotransmission in nucleus accumbens, compulsive drug intake and cue-induced drug craving after protracted abstinence appears to engage dorsal striatum. In fact, selective and hierarchical recruitment of striatal subregions has

been implicated in transition from recreational to compulsive drug use. Additionally, amphetamine-induced structural plasticity strengthens inputs to dorsolateral striatum (DLS), while weakens inputs to dorsomedial striatum (DMS), after protracted abstinence. Therefore, the aim of this study was to define progressive modulations in neuronal excitability and synaptic plasticity in the form of endocannabinoid-mediated long-term depression in dorsal striatal subregions after repeated administration of amphetamine. To this end, adult Wistar rats received five daily injections of amphetamine (2.0 mg/kg), and treatment effects on striatal neurotransmission was monitored by *ex vivo* slice electrophysiology for up to ten weeks of abstinence. We found that five days of amphetamine administration enhanced amphetamine-induced locomotion and rearing activity in a manner that sustained for at least 10 weeks. Measurement of evoked field excitatory post-synaptic potentials (fEPSPs) showed that amphetamine treatment depressed neuronal excitability in DMS and DLS in a temporal manner that was concurrent with a decrease in probability of neurotransmitter release. In addition, high frequency stimulation of afferent fibers of dorsal striatum revealed that endocannabinoid-mediated long-term depression was enhanced in the DLS of amphetamine-treated rats after protracted abstinence. In parallel, bath application of the dopamine D2 receptor agonist quinpirole (5 μM), depressed fEPSPs to a greater extent in slices from vehicle-treated rats as compared to rats treated with amphetamine ten weeks earlier. The data presented here suggests that passive administration of amphetamine initiates progressive reorganization of brain regions associated with goal-directed behavior and habitual performance, which continue to develop even after discontinuation of amphetamine administration. These neuroadaptations might contribute to the development of compulsive drug seeking and an increased susceptibility to relapse.

Disclosures: **A. Lotfi:** None. **O. Lagström:** None. **B. Söderpalm:** None. **M. Ericson:** None. **L. Adermark:** None.

Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA21699

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Title: Antagonism of neurotensin receptors in the ventral tegmental area decreases methamphetamine self-administration in mice

Authors: *S. DOMINGUEZ-LOPEZ[1], W. B. LYNCH[1], M. WOLLET[1], A. L. SHARPE[2], M. J. BECKSTEAD[1]
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Abstract: Neurotensin is a peptide found in the brain and known to modulate dopamine neurotransmission and dopamine-related behaviors. Recently, we reported that neurotensin depresses inhibitory post-synaptic currents mediated by dopamine D_2 autoreceptors in midbrain dopamine neurons, thus enhancing or potentiating dopamine neurotransmission. In line with this finding, the rewarding properties of neurotensin in the ventral tegmental area has been documented using electrical and optogenetic self-stimulation, showing that neurotensin is able to facilitated operant behavior. Here we test the hypothesis that neurotensin input in the ventral tegmental area facilitates methamphetamine self-administration in mice. For this, male DBA/2J mice were implanted with an indwelling catheter in the right jugular vein and a bilateral cannula in the ventral tegmental area. A week after surgery, mice were trained to nose-poke for an intravenous infusion of methamphetamine (0.1 mg/kg/infusion) in daily operant sessions of 2 h. Animals receiving microinfusions of the neurotensin receptor antagonist SR142948A in the ventral tegmental area (10 ng/per side), during the first five days of methamphetamine exposure, required on average more days of training to acquire methamphetamine self-administration ($P=0.0075$ vs. Saline). The SR142948A group also showed a decreased number of infusions during acquisition and stabilization of methamphetamine self-administration ($P<0.001$ vs. Saline). The effect induced by SR142948A was not related to changes in basal locomotor activity or changes in methamphetamine induced-locomotion. Our results suggest that neurotensin receptor activation in the ventral tegmental area facilitate acquisition of methamphetamine self-administration in mice.

Disclosures: S. Dominguez-Lopez: None. **W.B. Lynch:** None. **M. Wollet:** None. **A.L. Sharpe:** None. **M.J. Beckstead:** None.

Poster

703. Amphetamines: Neural Mechanisms of Addiction

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Topic: G.08. Drugs of Abuse and Addiction

Support: Z1A DA000389 21

Title: Discovery of novel DAT inhibitors based on the modafinil scaffold for the treatment of psychostimulant abuse

Authors: J. GIANCOLA[1], A. BONIFAZI[1], J. CAO[1], R. SLACK[1], A. GADIANO[1], R. RAIS[2], B. SLUSHER[2], *A. H. NEWMAN[1]
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Abstract: Methamphetamine is a highly addictive psychostimulant, yet to date, no pharmacological treatment is available for methamphetamine use disorders. Like methamphetamine, the clinically available and wake-promoting drug modafinil binds to the dopamine transporter (DAT); however, unlike methamphetamine, it has low abuse potential. Modafinil has been evaluated for the treatment of methamphetamine abuse with mixed results. We have recently developed several novel analogues, based on the modafinil scaffold (e.g. JJC8-016, JJC8-088, JJC8-089 and JJC8-091; Cao et al 2016, Zhang et al 2017) and tested them on intravenous methamphetamine self-administration in rats that were allowed short access (1 h; ShA) or long access (6 h; LgA) exposure to the drug (Ho et al, 2017). Although several analogues were effective, the analogue with highest binding affinity (Ki=2.6 nM) and selectivity for DAT (JJC 8-088) was least effective in these models of methamphetamine abuse, possibly due to its poor pharmacokinetics. Hence, we extended our structure-activity relationship study by chemically manipulating the oxidation state of the sulfoxide group and by replacing the metabolically susceptible piperazine ring of the JJC series with a variety of bioisosteres, resulting in several novel lead molecules. Evaluation for binding affinities at DAT, SERT and sigma-1 receptors led to the selection of a subset of compounds to be evaluated for metabolic stability in liver microsomes, as well as pharmacokinetic studies in rats. In total, these studies will serve to identify the next lead compound(s) for behavioral evaluation and development toward pharmacotherapeutic treatment of psychostimulant abuse.

Disclosures: J. Giancola: None. **A. Bonifazi:** None. **J. Cao:** None. **R. Slack:** None. **A. Gadiano:** None. **R. Rais:** None. **B. Slusher:** None. **A.H. Newman:** None.

Poster

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Training Grant GM060665

Title: Chronic voluntary oral Methamphetamine administration disrupts spatial-memory performance by producing a long-lasting neuroinflammatory response that disrupts synaptic protein trafficking in the hippocampus of adolescent mice

Authors: *D. SHOR[1], J. A. AVILA[1,3], R. ZANCA[1,3], N. PALEOLOGOS[1], A. ALLIGER[1], M. E. FIGUIEREDO-PEREIRA[2,3], P. A. SERRANO[1,3]
[1]Psychology, [2]Biol., Hunter Col., New York, NY; [3]The Grad. Ctr. of CUNY, New York, NY

Abstract: Methamphetamine (MA) is a neurotoxic drug of abuse that induces neurodegenerative processes in the brain affecting behavior and cognition. Previous studies have focused largely on examining MA-induced neurochemical and behavioral deficits by injecting high doses (30 mg/kg MA; Braren et al., 2014), identifying the upper limits of MA-induced neurotoxicity. Little is known about the lower limits of MA doses necessary to produce neurotoxicity and behavioral deficits. Accordingly, we have developed an appetitive model of voluntary oral MA administration (VOMA) in rodents based on the consumption of palatable oatmeal chips containing a known amount of MA. In the current VOMA study, mice were given new presentations of sweetened oatmeal chips containing 1 mg/kg MA every 15 min for 3h every day for 28 days. We show that mice on VOMA consumed on average 1.743 mg/kg bw MA/hour, and an average of 5.23 mg/kg bw MA/day over 28 consecutive days (an average of 146.4 mg/kg total MA over 28d). During a brief abstinence period, working memory and reference memory assessments on the radial arm maze revealed long-lasting spatial memory deficits after 28d of VOMA. To delineate the molecular mechanisms that 28d VOMA disrupts in the hippocampus, a brain region pivotal to spatial memory processing, we analyzed whole-hippocampi for changes in synaptic and neuroinflammatory marker expression. We hypothesize that increased neuroinflammation following VOMA disrupts the trafficking of synaptic plasticity markers in the hippocampus, which leads to cognitive deficits in-vivo. Our results show that 28d of VOMA significantly increases expression of neuroinflammatory markers GFAP and COX2, and decreases levels of prostaglandins (PG) D2 and E2. Expression of highly neurotoxic PGJ2 was unchanged, suggesting that 28 days of VOMA induces a prolonged but not chronic neuroinflammatory response in the hippocampus. PKMζ, GluA2, and PSD95, markers pivotal to synaptic plasticity and memory in-vivo, were significantly decreased after 28d VOMA. This suggests that the prolonged neurotoxicity of 28d VOMA, despite not elevating PGJ2, is sufficient to disrupt synaptic plasticity that results in poor memory performance in-vivo. 28d of VOMA also disrupted dopaminergic function in the hippocampus by decreasing TH and DAT expression, effects observed in previous models. Our data reveal that 28d of VOMA produces a prolonged increase in markers of neuroinflammation and decreased expression of markers necessary for synaptic plasticity and spatial memory processing in the hippocampus. Future studies will evaluate the progression of this neurotoxic state using the VOMA model in male and female mice.

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Poster

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Training Grant GM060665

Title: Two-weeks of voluntary oral Methamphetamine administration produces acute spatial-memory deficit and increases chronic neuroinflammatory activity in the hippocampus of adolescent male C57Bl6 mice during abstinence

Authors: *J. A. AVILA[1,3], D. SHOR[1], F. TAVERNIER[1], R. M. ZANCA[1,3], D. ALVARADO-MATEO[4], A. TANG[1], M. E. FIGUEIREDO-PEREIRA[2,3], P. A. SERRANO[1,3]
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Abstract: Methamphetamine (MA) is a neurotoxic drug of abuse producing neurodegenerative processes that impair cognition. The mechanisms that produce neurotoxicity and cognitive deficits following MA abuse have been characterized in bolus-dose models (Braren et al., 2014), in which high doses are administered acutely. However, little is known about the lower limits of MA doses necessary to produce these deficits. Additionally, it is unclear how chronic dosing and, separately, abstinence, contribute to the progression of these deficits. To understand these features of MA abuse, we have developed a novel rodent voluntary oral administration model of MA (VOMA), with presentations of oatmeal chips containing 1 mg/kg MA for oral consumption. In the current study, adolescent male C57Bl6 mice received MA presentations every 15 min during 4h every day for 14 days. Following VOMA, mice underwent a forced-abstinence period, during which we assessed spatial-memory performance on the radial arm maze (RAM), depressive phenotype using a tail-suspension test, and VOMA-induced contextual sensitization. Following behavioral assessments, we analyzed whole hippocampi for expression of synaptic and neuroinflammatory markers. Tracking of MA consumption revealed two distinct consumer groups. High-consuming mice consumed an average of 0.765 mg/kg bw MA/hr and an average of 3.059 mg/kg bw MA/day over 14d (average of 42.833 mg/kg bw MA total over 14d). Low-consuming mice consumed an average of 0.346 mg/kg bw MA/hr and an average of 1.385 mg/kg bw MA/day over 14d (average of 19.4 mg/kg bw MA total over 14d). Contextual sensitization measures showed that mobility before VOMA delivery is increased in High-consuming mice at 8d of VOMA, and decreases in the same group at the end of the 14d VOMA

period. RAM assessments revealed an acute spatial working memory deficit in High-consuming mice following VOMA. Prolonged abstinence rescued this memory deficit in a subsequent 10-day learning assessment on the RAM. Preliminary molecular analyses have revealed that abstinence increases expression of COX-2 and highly neurotoxic PGJ2 in mice hippocampi, suggesting that susceptibility to chronic neuroinflammation increases after MA abuse has ended. VOMA accurately models voluntary MA abuse in humans by producing discreet consumer populations in mice that exhibit acute and dose-dependent cognitive deficits. Additionally, our data have revealed that abstinence promotes the development of chronic neuroinflammatory pathways in the hippocampus despite evading prolonged cognitive dysfunction. Current work is examining the behavioral and neurochemical responses to this paradigm in female mice.

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Poster

703. Amphetamines: Neural Mechanisms of Addiction

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 703.09/RR16

Topic: G.08. Drugs of Abuse and Addiction

Title: Regulation of calcium binding proteins in the anterior cingulate area correlates with methamphetamine addiction and maladaptive sexual behavior

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Abstract: It is well known that drugs of abuse and natural rewards affect common brain circuitry, and that drug use in a socio-sexual context leads to compulsive sex- and drug-seeking behaviors. Our laboratory has demonstrated that concurrent experience with methamphetamine (Meth) and sexual behavior increases relapse to Meth seeking and resistance to extinction, as well as maladaptive sexual behavior. CaMKII-immunoreactive projection neurons in the anterior cingulate area (ACA) of the medial prefrontal cortex play a key role as Meth and sex co-activate these cells and chemogenetic inhibition during Meth and sex experience prevents increased relapse vulnerability. Moreover, concurrent Meth and sex experience causes long-lasting increases in basal neuronal activity of these cells, as evidenced by increased phosphorylation of MAP kinase. The current study tests the hypothesis that the effect of concurrent Meth/sex on neuronal activity of CaMKII cells in the ACA is accompanied by alterations in expression of calcium binding proteins in GABAergic inhibitory neurons. Male rats received Meth (1 mg/mL/kg s.c.) or saline and mated to one ejaculation (Meth/sex or sal/sex) for 4 consecutive

days. In addition, males received non-concurrent Meth or saline and mating experience: 4 consecutive days of mating, followed by 4 consecutive days of drug treatment (Meth or sal). One week after the final treatment session, animals were taken from their home cage and perfused. Immunohistochemistry was performed to visualize parvalbumin, calretinin, and calbindin, which are expressed in inhibitory interneurons. Cell were counted in the ACA. Results showed that concurrent Meth/sex significantly decreased the numbers of neurons labeled for parvalbumin, but not calretinin or calbindin, compared to the sal/sex concurrent group. Non-concurrent exposure to sex and Meth did not affect immunoreactivity, nor did sexual experience alone. This reduction of parvalbumin neurons may lead to reduced inhibition of ACA pyramidal cells. Further research will investigate the loss of parvalbumin inputs on pERK-immunoreactive CaMKII neurons. Together, these results demonstrate a synergistic effect of Meth and sex on neuroplasticity in ACA interneurons. Closer investigation of the molecular mechanisms leading to this plasticity will help us better understand how drug use in a socio-sexual context leads to vulnerability for drug addiction and hypersexuality.

Disclosures: L.B. Kuiper: None. **L.M. Coolen:** None.

Poster

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Program#/Poster#: 703.10/RR17

Topic: G.08. Drugs of Abuse and Addiction

Title: Methamphetamine and psychological stress activate corticotropin-releasing factor receptor 1 cells in a sex dependent manner

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Abstract: Corticotropin releasing factor (CRF) and specifically it's binding to the CRFR1 receptor subtype has repeatedly been shown to play a key role in drug-related behaviors including drug seeking, self-administration, and reinstatement after withdrawal. Sex differences in patterns of methamphetamine (MA) abuse have been observed in humans and rodents. Women begin using MA at an earlier age, are more committed to MA, and show an accelerated spiral into MA addiction compared to men. In addition, female rodents show greater MA seeking and reinstatement following a withdrawal period. Because MA is a potent activator of the hypothalamic-pituitary-adrenal (HPA) axis and is known to stimulate the brain CRF system, we hypothesized that exposure to MA would activate CRFR1 cells, and this effect would differ between males and females. To test this, C57BL6J CRFR1 reporter mice were i.p. injected with MA (5 mg/kg) and sacrificed 120 minutes later when brains were collected. Co-localization of

transcription/neuronal activation marker phosphorylated CREB (pCREB) with CRFR1 in stress responsive brain regions was assessed via immunohistochemistry. Our previous work has shown that MA increases neural activation in stress responsive brain regions in a pattern distinct from psychological stress. Therefore, another cohort of mice was restraint stressed for 30 minutes to compare levels of CRFR1 cell activation between psychological stress and MA exposure. In the rostral anteroventral periventricular hypothalamus (AVPV/PeN) and central amygdala (CeA) restraint stress increased co-localization more so in females. MA increased co-localization of pCREB with CRFR1 in the medial preoptic area (MPOA) and AVPV/PeN in females more than males. In the paraventricular hypothalamus (PVN), MA increased co-localization to a greater extent in males. These findings suggest that CRFR1 expressing cells are differentially activated by psychological stress versus MA. Furthermore, these effects appear to be sex dependent, suggesting that these differences may underlie observed sex differences in behavioral patterns of drug abuse. Future studies will seek to determine the extent to which CRFR1 expressing cells contribute to sex differences in addiction-like behaviors.

Disclosures: J. Jacobskind: None. **Z.J. Rosinger:** None. **N.J. Justice:** None. **D.G. Zuloaga:** None.

Poster

703. Amphetamines: Neural Mechanisms of Addiction

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Program#/Poster#: 703.11/RR18

Topic: G.08. Drugs of Abuse and Addiction

Title: The anterior insula→central amygdala glutamatergic pathway is critical to relapse after contingency management

Authors: *M. ZHANG[1], D. CAPRIOLI[2], L. R. WHITAKER[1], S. ZHANG[1], B. L. WARREN[1], C. CIFANI[3], N. J. MARCHANT[4], O. YIZHAR[5], J. M. BOSSERT[1], C. CHIAMULERA[6], M. MORALES[1], Y. SHAHAM[1], M. VENNIRO[1]
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Abstract: Background: We recently developed a rat model of relapse after choice-based voluntary abstinence that mimics human relapse after cessation of contingency management, a behavioral treatment that uses alternative non-drug rewards to maintain abstinence. Here, we studied the role of central amygdala (CeA) and its afferent projections in relapse after voluntary abstinence.
Methods: We trained rats to self-administer palatable food (6 d) and intravenous

methamphetamine (14 d). We then assessed relapse to methamphetamine seeking after 14 voluntary abstinence days (achieved via a discrete choice procedure between methamphetamine and palatable food).
Results: Relapse to methamphetamine seeking after voluntary abstinence was associated with increased expression of the activity marker Fos in CeA but not basolateral amygdala (BLA). Systemic injections of the dopamine Drd1-family receptor antagonist SCH39166 decreased relapse and CeA Fos expression; in situ hybridization showed higher co-labeling of Fos with Drd1 than with Drd2. CeA SCH39166 injections decreased relapse after voluntary abstinence; in contrast, BLA SCH39166 injections or CeA injections of the dopamine Drd2-family receptor antagonist raclopride were ineffective. Double-labeling of Fos with the retrograde tracer cholera toxin subunit-B (CTb, injected in CeA) demonstrated that relapse after voluntary abstinence was associated with selective activation of ventral anterior insula (AIV)→CeA projection. AIV inactivation with GABA receptor agonists or chemogenetic inactivation of AIV→CeA projection decreased relapse after voluntary abstinence. Electron microscopy data showed that AIV vGluT1-expressing projection-neurons form excitatory asymmetric synapses on CeA neurons.
Conclusions: Our data demonstrate a critical role of CeA Drd1 and the AIV→CeA glutamatergic projection in relapse after cessation of contingency management-induced voluntary abstinence.
This work was supported by NIDA/NIH.

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Poster

703. Amphetamines: Neural Mechanisms of Addiction

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Program#/Poster#: 703.12/RR19

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Intramural Program

Title: Role of anterior intralaminar nuclei of thalamus projections to dorsomedial striatum in incubation of methamphetamine craving

Authors: *X. LI[1], K. WITONSKY[1], F. SURJONO[1], J. ZHANG[2], J. M. BOSSERT[1], Y. SHAHAM[1,2]
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Abstract: Background: Methamphetamine seeking progressively increases after withdrawal from drug self-administration (incubation of methamphetamine craving). We previously demonstrated an important role of dorsomedial striatum (DMS) activity in this incubation. Here, we studied the role of glutamatergic and dopaminergic afferent projections to DMS in incubation of methamphetamine craving.
Methods: We trained rats to self-administer methamphetamine (6-h/d for 10 d) and then tested for relapse to drug seeking after 1 or 30 withdrawal days. In Exp.1, we measured projection-specific activation on withdrawal day 30 relapse test, using double-labeling of cholera toxin subunit B (retrograde tracer, injected into DMS)+Fos (neuronal activity marker) in cell bodies of the projection areas. Based on Exp. 1 results, we determined the effect of reversible inactivation [muscimol+baclofen(GABAa+GABAb agonists), 3+15 ng/0.3 µl/side] of the anterior intralaminar nuclei of thalamus (AIT) on incubated (day 30) methamphetamine seeking (Exp. 2). Next, we used an anatomical disconnection procedure [muscimol+baclofen injection (3+15 ng/0.3 µl/side) into AIT; SCH23390 (Drd1 antagonist) injection into DMS (0.75 µg/0.5 µl/side)] to determine the role of the AIT-to-DMS projection in incubated methamphetamine seeking (Exp. 3).
Results: Incubated methamphetamine seeking was associated with activation of the AIT-to-DMS projection but not other projection areas. Bilateral (but not unilateral) AIT inactivation, and both contralateral and ipsilateral disconnection of the AIT-to-DMS projection decreased incubated methamphetamine seeking.
Conclusions: Results demonstrate that the AIT and its projection to DMS plays a critical role in incubation of methamphetamine craving. Our results also suggest a novel role of the AIT-to-DMS projection in drug addiction and other motivated behaviors.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA025634

Title: Chemogenetic inhibition of dopamine neurons reveals phasic dopamine release as a critical substrate for amphetamine induced dopamine activation and hyperlocomotion

Authors: *S. M. CONWAY[1,2], M. F. ROITMAN[1]
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Abstract: Amphetamine (AMPH) is thought to increase extracellular dopamine concentrations in the nucleus accumbens (NAc) primarily through action at dopamine terminals. Characterized as a dopamine releaser in *in vitro* studies, AMPH invades the presynaptic terminal via the dopamine transporter (DAT), compromises vesicular packaging, and increases extracellular dopamine through reverse transport. As such, AMPH activates nonexocytotic dopamine release and eliminates the ability of dopamine neurons to phasically signal through exocytotic release. Yet, AMPH increases the frequency of phasic dopamine release events (dopamine transients) *in vivo*, a signaling pattern inconsistent with reverse transport. Thus, our study seeks to determine the extent to which AMPH-induced increases in NAc dopamine and hyperlocomotion target phasic dopamine release signaled by neural activity at the dopamine cell bodies in the ventral tegmental area (VTA). While the reverse transport model predicts nonexocytotic dopamine activation occurs independent of VTA neural activity, we predicted that inhibition of VTA dopamine activation would attenuate AMPH-induced increases in NAc dopamine transients and hyperlocomotion. To achieve inhibitory control of VTA dopamine neurons, we virally delivered the Cre-dependent inhibitory (hM4Di) designer receptor exclusively activated by designer drug (DREADD) to transgenic rats expressing Cre recombinase under control of the tyrosine hydroxylase promotor (TH:Cre+) and wildtype littermates (TH:Cre-). In this manner, hM4Di expression is restricted to VTA dopamine neurons in TH:Cre+ rats, and using fast-scan cyclic voltammetry, we show that systemic administration of the DREADD ligand, clozapine-n-oxide (CNO) suppressed electrically evoked phasic dopamine release only in TH:Cre+ rats. We went on to measure changes in the frequency of dopamine transients in the NAc in response to AMPH (2.5 mg/kg, IP). Similar to recent work in behaving rats, we observed AMPH-induced increases in dopamine transient frequency. This effect was significantly reduced with CNO pretreatment (1 mg/kg, IP) relative to vehicle in TH:Cre+ rats, results consistent with the idea that AMPH activates exocytotic dopamine release in behaving rats. Furthermore, we have observed a suppression in AMPH-induced hyperlocomotion with systemic CNO to TH:Cre+ rats. Future work aims to determine the precise anatomical site along the mesolimbic pathway underlying these effects by repeating locomotor testing using intra-VTA CNO delivery. Taken together, these results corroborate *in vivo*-based conclusions supporting VTA dopamine activity as a critical target for AMPH action.

Disclosures: S.M. Conway: None. **M.F. Roitman:** None.

Poster

703. Amphetamines: Neural Mechanisms of Addiction

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Topic: G.08. Drugs of Abuse and Addiction

Support: Valley Research Partnership Grant, AZ

Title: Virus-mediated inactivation of GluA1 in ventral tegmental area dopamine neurons prevents social stress-induced psychostimulant cross-sensitization in rats

Authors: *M. L. RUDOLPH[1,2], R. N. HENDERSON[1], R. L. NEVE[3], R. P. HAMMER[1,2], E. M. NIKULINA[1]
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Abstract: Evidence from both human and animal studies demonstrates the importance of social stress in the development of addiction-related behavior. In rats, social defeat stress induces long-lasting social avoidance and psychostimulant cross-sensitization. Our recent data reveal heightened expression of AMPA receptor GluA1 subunit in rat ventral tegmental area (VTA) tissue, which occurs concurrently with social stress-induced amphetamine cross-sensitization. The objective of the present study was to determine whether social stress induces GluA1 expression primarily in dopamine cells, and to examine whether GluA1 is necessary for social stress-induced behaviors. Male Sprague Dawley rats that express Cre-recombinase under the control of an endogenous TH promoter, were exposed to aggressive Long-Evans rats four times over a period of 10 days; control rats were handled at the same times. Such intermittent social stress exposure increased GluA1 expression in VTA dopamine neurons as evidenced by a greater density of GluA1/TH double-labeling in VTA neurons of rats subjected to social stress compared to handling. In order to examine whether GluA1 is necessary for the effects of social stress, a Cre-dependent dominant negative pore-dead GluA1 construct packaged in AAV (AAV-pd-GluA1) was used to selectively reduce GluA1 function in TH neurons. The viral construct was bilaterally infused into the VTA three weeks before rats were subjected to social defeat stress; control rats had sham surgeries. Behavioral testing was performed 10-14 days after stress termination. Amphetamine (1.0 mg/kg i.p.) challenge significantly augmented locomotion in rats with normal GluA1, while virus-mediated overexpression of AAV-pd-GluA1 prevented amphetamine cross-sensitization. By contrast, in the three-chamber approach/avoidance test, functional inactivation of GluA1 did not affect stress-induced social avoidance. Taken together, these results suggest that GluA1 expression in VTA dopamine neurons is necessary for stress-induced psychostimulant cross-sensitization, but not for stress-induced social avoidance. This differential effect suggests that different neural pathways may be implicated in these behaviors. Clarifying such cellular mechanisms of social stress-induced cross-sensitization may be critical to the development of therapeutic agents for the treatment of stress-induced substance abuse susceptibility.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH NIDA Intramural Research Program

Title: Compulsive methamphetamine taking is associated with increased CARTpt expression in the rat dorsal striatum

Authors: *J. L. CADET, I. KRASNOVA, S. JAYANTHI, B. LADENHEIM, M. MCCOY
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Abstract: Methamphetamine addiction is a common neuropsychiatric disorder that affects a vast number of people throughout the world. Addiction can be mimicked, in part, by using drug self-administration paradigms in several animal species including rodents. Nevertheless, addiction is actually more than self-administration because addiction includes the presence of adverse consequences as a criterion to reach that diagnosis in humans. Recently, we have begun to include footshocks as adverse consequences to influence drug self-administration by rats. We trained rats to self-administer methamphetamine for 20 days. All rats escalated their methamphetamine intake during this training phase. Thereafter, 50 percent of lever presses were punished by mild footshocks for 5 days. Response-contingent punishment reduced methamphetamine taking in some rats (shock-sensitive, SS) but not in others (shock-resistant, SR). Rats also underwent extinction test at one day and 30 days after the last shock session to test if there were increases in lever pressing in the absence of methamphetamine. Rats were euthanized one day after the second extinction test to collect striatal tissues to measure genome-wide transcriptional consequences of methamphetamine SA and footshocks in rat brain. At the second extinction test, shock-resistant rats showed significantly higher incubation of methamphetamine craving than punishment-sensitive rats. We found significant increases in striatal CARTpt mRNA in the shock-resistant rats by both microarray and PCR analyses. These observations support a potential role of striatal CARTpt in incubation of methamphetamine seeking after a long withdrawal interval. These findings also suggest that treatment approaches that impact this neuropeptidergic system might be beneficial to methamphetamine-addicted individuals.

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Poster

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WVU E.J. Van Liere Medicine Professorship

Title: RGS12 modulates the dopamine transporter in ventral striatum and locomotor responses to psychostimulant drugs-of-abuse

Authors: *J. D. GROSS, S. W. KASKI, A. B. SCHROER, K. WIX, D. P. SIDEROVSKI, V. SETOLA
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Abstract: The Regulators of G protein Signaling comprise a family of intracellular proteins that accelerate the termination of effector stimulation after G protein-coupled receptor (GPCR) activation. RGS12 is the most complex family member, with at least five different functional motifs. Surveying RGS12 expression in various brain tissues, we have found marked expression in the mouse ventral striatum. Given the role of the ventral striatum in psychostimulant-induced locomotor activity, we tested whether RGS12 function is involved in amphetamine- and cocaine-stimulated hyperlocomotion. RGS12 loss resulted in decreased hyperlocomotion to lower doses of both psychostimulants; however, outcomes of repeated administration (sensitization and conditioned place preference) were unaffected. To test whether RGS12 might have a role in dopamine transporter (DAT) expression and/or function, we prepared crude membranes from the brains of wild type and *Rgs12*-null mice and measured DAT-selective [^{3}H]WIN 35428 binding, revealing an increase in DAT levels in the ventral—but not dorsal—striatum of *Rgs12*-null mice compared with wild type tissue. To address whether this increase in DAT expression translated into increased DAT function, we prepared ventral striatal synaptosomes and measured [^{3}H]dopamine uptake. Consistent with increased [^{3}H]WIN 35428 binding, DAT-specific [^{3}H]dopamine uptake in RGS12-null ventral striatal synaptosomes was increased compared with wild type preparations. Observations of decreased psychostimulant-induced locomotor activity, increased [^{3}H]WIN 35428 binding, and DAT-specific [^{3}H]dopamine uptake were recapitulated with an independent *Rgs12*-null mouse strain. RGS12 is thus a previously unidentified negative

regulator of DAT expression and function in the ventral striatum, affecting psychostimulant-induced increases in dopamine levels that specifically elicit acute hyperlocomotor responses.

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Poster

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Program#/Poster#: 703.17/RR24

Topic: G.08. Drugs of Abuse and Addiction

Title: A possible role of orexin signaling pathway in methamphetamine-mediated drug addiction

Authors: C. LEE[1], G. PARK[2], *J.-H. JANG[1]
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Abstract: Methamphetamine (METH) is a powerful neurotoxic psychostimulant affecting dopamine transporter (DAT) activity and leading to blockage of dopamine reuptake, which results in continuous excess extracellular dopamine levels between pre- and post-synaptic neurons. In this study, we have tried to elucidate a new molecular regulator involved in METH-induced reward and drug addiction. METH (1 mg/kg/day, *i.p.*) was injected to C57BL/6 mice for four alternative days and locomotor as well as conditioned place preference (CPP) tests were performed as behavior analysis. Markers of dopamine system integrity and changes of orexin-related signaling molecules were examined to investigate underlying mechanisms. Orexin has been reported to play a crucial role in the regulation of arousal, wakefulness, and motivated behavior for drug abuse. METH-administered group exhibited increased locomotor activity and sensitivity to place preference compared with saline-treated control group on locomotor and CPP tests, respectively. METH significantly decreased dopamine-related markers such as DAT, dopamine 2 receptor (D2R), and tyrosine hydroxylase (TH). Conversely, METH increased expression levels of orexin and orexin-1 receptor particularly in the brain regions of hypothalamus and amygdala. Moreover, METH caused oxidative stress and neuronal damages by increasing lipid peroxidation and decreasing antioxidant defense capacity. These findings suggest that orexin may play a role for the behaviors associated with reward and/or reinforcement of METH and disrupt dopamine neurotransmissions via augmentation of oxidative neuronal damages.

Disclosures: C. Lee: None. **G. Park:** None. **J. Jang:** None.

Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 DA09397

Title: Phosphorylation by PKC but not PKA of AMPA receptor GluA1 subunit residues in the nucleus accumbens is required for expression of sensitized amphetamine-induced locomotion and self-administration

Authors: *P. VEZINA, J. BROWN, N. NEUGEBAUER, K. RODVELT, D. LI, N. BUBULA, P. MASCIA
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Abstract: Recently we reported that basal phosphorylation by PKA of an AMPA receptor GluA1 subunit residue in the rat nucleus accumbens (NAcc) was increased weeks following sensitizing exposure to amphetamine, suggesting a potential role in the expression of sensitization by this drug. Here we report that when amphetamine exposed rats were challenged with the drug, a condition necessary for the expression of sensitization, PKA activity was surprisingly reduced in this site. Conversely, no change in phosphorylation by PKC of GluA1 subunit residues was detected basally weeks following amphetamine exposure. However, when rats were challenged with amphetamine, PKC activity was increased. Together, these results suggest that phosphorylation by PKC but not PKA in the NAcc is required for the expression of amphetamine sensitization. To assess this possibility, rats in different groups were exposed to 5 injections of amphetamine (1.5 mg/kg, IP; 1 injection every other day). One week later, they were infected in the NAcc with lentivirus bearing GFP or the serine-alanine mutants GluA1(S845A) or GluA1(S816A-S818A). Phosphorylation of these PKA and PKC residues, respectively, is known to facilitate GluA1 insertion into the plasma membrane which in turn can enhance glutamatergic transmission and enable the expression of sensitization by amphetamine. Two weeks following infection, rats in one experiment were tested for their locomotor response to NAcc amphetamine (2.5 µg/side). Rats in a second experiment were prepared with an IV catheter and given the opportunity to self-administer amphetamine (100 µg/kg/infusion) on a PR schedule of reinforcement. Preventing GluA1 phosphorylation by PKC blocked expression of the sensitized locomotor response to NAcc amphetamine as well as the enhanced self-administration of IV amphetamine normally observed in rats exposed to the drug. Remarkably, preventing phosphorylation by PKA spared enhanced responding to (locomotion) and for the drug (self-administration). These results, consistent with the biochemical profiles of PKA and PKC activity observed following exposure to amphetamine, support the need for NAcc PKC but not PKA

phosphorylation in the expression of behavioral sensitization by amphetamine and highlight the importance of NAcc AMPA receptor regulation by PKC in generation of the sensitized response.

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Title: The brain mechanisms of methamphetamine-induced behavioral sensitization: Nucleus accumbens core and shell

Authors: *C.-N. CHENG[1,2], C. A. HUANG[1]
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Abstract: Abused drugs have been shown to underlie the brain mesolimbic dopamine system to result in drug addiction. In particular, some studies suggested that the nucleus accumbens of the mesolibmic dopamine system is essential for drug addiction. However, whether the brain subareas of nucleus accumbens including nucleus accumbens core and shell play separate roles the development of drug addiction remains unclear. The present study focuses on this issue. Initially, half of all rats were injected a high dose of NMDA to destroy nucleus accumbens shell or core. After 7 days for recovery, all of rats were continuously administrated with methamphetamine (MAMPH, 1mg/kg) or vehicle (normal saline), and then they were assigned into Saline and MAMPH groups (n = 16, per group) one trial a day for 7 days. Later, the withdrawal phase was conducted for 7 days. After that, a low dose of methamphetamine (0.5mg/kg) was challenged to measure the locomotor activity. The results showed that MAMPH induced hyperactivity for behavioral sensitization in drug addiction.
NMDA injections interfered with behavioral sensitization and showed decreased locomotor activity on test phase. NMDA injections did not affect locomotor activity for behavioral sensitization during the sensitization acuqisition phase. For nucleus accumbens shell, during acquisition phase, NMDA injections into the nucleus acumens shell would facilitate locomotor activity for behavioral sensitization. During testing, NMDA injection into the shell of the nucleus accumebns probably increased locomotor activity. Some findings of the present study for drug addiction and dependence need to be discussed further.
Keywords: nucleus accumbens shell, nucleus accumbens core, dopamine, behavioral

sensitization, methamphetamine
Grand Support: MOST 105-2410-H-431-005

Disclosures: C. Cheng: None. **C.A. Huang:** None.

Poster

703. Amphetamines: Neural Mechanisms of Addiction

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: G.08. Drugs of Abuse and Addiction

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Title: Repeated exposure of adolescent mice to 3,4-methylenedioxypyrovalerone activates transcriptional mechanisms that persist until adulthood and are similar to those activated by cocaine

Authors: L. DUART-CASTELLS[1], *M. H. BUENROSTRO-JAUREGUI[2], P. MUÑOZ-VILLEGAS[3], R. LÓPEZ-ARNAU[1], J. CAMARASA[1], D. PUBILL[1], E. ESCUBEDO[1]
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Abstract: 3,4-Methylenedioxypyrovalerone (MDPV) is a new synthetic cathinone with psychostimulant properties. It selectively blocks the dopamine transporter (DAT), similarly to cocaine, but with higher potency. Moreover, in mice, an early (adolescence) exposure to MDPV induces long-lasting adaptive changes that lead to a major responsiveness and vulnerability to cocaine in adulthood. Accordingly, it is of interest to describe which transcriptional mechanisms are activated after a chronic exposure to MDPV (1.5 mg/kg, s.c., twice daily for 7 days) once the treatment is finished, 21 days after (adulthood), and after a saline or cocaine (7.5 mg/kg, i.p.) challenge administered at the end of the withdrawal. In parallel, behaviors such as anxiety and impulsivity once the drug was withdrawn were assessed by the elevated plus maze (EPM) and the open field test (OF), respectively. The expression of several factors in the striatum was

determined by Western blot and radioligand binding assays. Dopamine receptor 1 (DR1), activity-regulated cytoskeleton-associated protein (Arc), cyclin-dependent kinase 5 (CDK5), ΔFosB and tyrosine hydroxylase (TH) levels were increased just after the treatment. Interestingly, after 21 days of withdrawal a few markers still remained altered compared with the control group: CDK5, ΔFosB and TH remained increased while DR1 and Arc decreased. In any case the exposure to MDPV altered the effects of a cocaine challenge on the expression of those factors. 4-hydroxynonenal (4-HNE) and glial fibrillary acidic protein (GFAP) levels were also determined in the dorsal striatum in order to assess any possible neurotoxic effect of MDPV. Only 4-HNE was significantly increased 24h post-treatment, possibly due to the synaptic oxidation of dopamine, while no change was observed in GFAP. Regarding the behavioral tests, no anxious-behavior was observed in the EPM neither 48h nor 21 days after treatment. Furthermore, 21 days after treatment, the OF test results suggest an increased impulsive-behavior in MDPV-treated mice since they explored more time the central area of the arena. In conclusion, repeated MDPV exposure during adolescence activates transcriptional mechanisms similar to those described after chronic cocaine exposure. Some of them persist until adulthood. These results explain our previous findings about the effect of MDPV on the behavioral responses related to cocaine effects, including locomotor sensitization, reward and the strength of cocaine as a reinforcer. In addition, the increased expression of ΔFosB in the orbito-frontal cortex in MDPV-treated mice could be correlated with the major impulsivity observed after 21 days of withdrawal.

Disclosures: **L. Duart-Castells:** None. **M.H. Buenrostro-jauregui:** None. **P. Muñoz-Villegas:** None. **R. López-Arnau:** None. **J. Camarasa:** None. **D. Pubill:** None. **E. Escubedo:** None.

Poster

704. Cocaine Seeking and Reinstatement I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 704.01/RR28

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA037744

Title: Roles for prelimbic prefrontal cortex projections to nucleus accumbens or rostromedial tegmental nucleus in cue-induced reinstatement of cocaine seeking

Authors: *L. S. LAIKS[1], T. H. KIM[2], T. C. JHOU[3], R. J. SMITH[1]
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Abstract: Distinct sublayers within the prelimbic (PL) area of prefrontal cortex project to nucleus accumbens (NAc) core and rostromedial tegmental nucleus (RMTg), two structures that often have opposing influences on cocaine-seeking behavior. We hypothesized that PL projections to RMTg play an inhibitory role in cue-induced reinstatement of cocaine seeking, in contrast to the well-established role for PL projections to NAc core in driving reinstatement. Here, we used a contralateral disconnection technique to test this hypothesis. Male Sprague Dawley rats self-administered intravenous cocaine paired with discrete tone and light cues for 10 days (0.2 mg/infusion; fixed ratio 1). After animals reached a criterion for extinction of responding in the absence of cocaine and cues, reinstatement was elicited by the tone and light cues. Prior to cue-induced reinstatement of cocaine seeking, rats were given microinjections of the GABA receptor agonists baclofen/muscimol into unilateral PL and the AMPA receptor antagonist NBQX into contralateral NAc core or RMTg, or were given vehicle microinjections. Preliminary findings indicate that cue-induced reinstatement was decreased by disconnection of PL and NAc, and increased by disconnection of PL and RMTg. Further study of both the behavioral function and anatomical connectivity of these distinct PL pathways is necessary to understand the role that PFC dysfunction plays in addiction.

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Poster

704. Cocaine Seeking and Reinstatement I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 704.02/RR29

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA037744

Title: Goal-directed and habitual cocaine seeking using ratio and interval schedules of reinforcement

Authors: *R. J. SMITH[1], T. H. KIM[2], H. F. SPENCER[1]
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Abstract: Ratio and interval schedules of reinforcement have been shown to generate goal-directed and habitual responding, respectively, for food and alcohol. However, it is unclear whether these different schedules will also generate goal-directed and habitual responding for cocaine. To assess instrumental response strategy, we developed an outcome devaluation procedure for intravenous cocaine using sensory-specific satiety. Male Sprague Dawley rats were trained on a seeking-taking chained schedule of cocaine self-administration, in which presses on a seeking lever gave access to a separate taking lever reinforced with intravenous cocaine (0.5

mg/kg/infusion). The seeking link of the chain required completion of a random ratio (RR20) or random interval (RI60) schedule, and the taking link was reinforced under a fixed ratio (FR1) schedule. Outcome devaluation was carried out via administration of non-contingent intravenous cocaine, followed by evaluation of responding on the seeking lever for 10 minutes under extinction conditions. We found that animals trained on a random ratio schedule were sensitive to outcome devaluation, indicating goal-directed behavior. In contrast, animals trained on a random interval schedule were insensitive to outcome devaluation, indicating habitual behavior. Further experiments showed that pre-training lesions of dorsomedial striatum caused rats to be insensitive to cocaine devaluation regardless of schedule, whereas pre-training lesions of dorsolateral striatum caused rats to be sensitive to cocaine devaluation. Given established roles for dorsomedial and dorsolateral striatum in goal-directed and habitual behavior, these data support the validity of this outcome devaluation procedure developed for intravenous cocaine. Altogether, these findings indicate that different schedules of reinforcement generate a bias toward goal-directed or habitual responding for cocaine.

Disclosures: **R.J. Smith:** None. **T.H. Kim:** None. **H.F. Spencer:** None.

Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant 5R00DA035251-05

NIH Grant R25GM055246

Title: Ventral pallidum roles in mixed appetitive/aversive motivational states related to cocaine relapse

Authors: *M. R. FARRELL, C. RUIZ, H. SCHOCH, E. CASTILLO, C. KHANBIJIAN, S. LIU, S. V. MAHLER
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Abstract: In drug-addicted individuals, abstinence is generally voluntarily chosen, often due to negative consequences associated with drug use, but many current animal models fail to emulate this aspect of relapse. Here, we model cocaine relapse after punishment-induced abstinence (modified from (Marchant et al., 2013)), in which rats voluntarily cease cocaine self-administration due to negative consequences associated with drug taking (i.e., lever-press contingent footshock). Male and female Long-Evans rats were trained to lever press to self-administer i.v. cocaine and discrete light+tone cue (increasing on a variable interval schedule) in

context A for 14 days. Then they were moved to context B, in which lever presses yielded cocaine and cues, but also a mild footshock on 50% of trials. Training continued until all animals showed voluntary suppression of seeking. Reinstatement of cocaine seeking was then tested under three conditions: in context A with response-contingent cues (but no cocaine), in context A without cues, and in context B with cues. To characterize roles for ventral pallidum (VP) in reinstatement following voluntary abstinence, we examined 1) activation of VP cells during reinstatement, and 2) effects of chemogenetic (DREADD) inhibition of VP on punished cocaine seeking and reinstatement behavior. We found that c-Fos analysis of VP activity varied by behavioral group, and VP subregion. We also found that VP inhibition with DREADDs blocked both context- and context+cue-induced reinstatement following abstinence, and modestly affected punished cocaine seeking as well. Finally, we characterized effects of chemogenetic VP inhibition on cocaine-induced locomotor behavior. These results indicate a novel role for VP in context- and cue-induced reinstatement to cocaine seeking in a translationally-relevant punishment-based model, and provide clues as to the complex and heterogeneous role for VP subpopulations in mixed appetitive/aversive motivational states related to cocaine relapse.

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Poster

704. Cocaine Seeking and Reinstatement I

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Support: WSU Alcohol & Drug Abuse Research Program Grant 124777 to Jordan M. Blacktop

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Title: Role of anterior dorsal lateral hypothalamic area perineuronal nets in cue-induced reinstatement of cocaine-seeking behavior

Authors: *J. M. BLACKTOP, B. A. SORG
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Abstract: Addiction involves drug-induced neuroplasticity of the circuitry of motivated behavior, which includes the medial forebrain bundle and the lateral hypothalamic area. Emerging at the forefront of neuroplasticity regulation are specialized extracellular matrix structures that form perineuronal nets (PNNs) around certain neurons, mainly parvalbumin positive (PV^+) fast-spiking interneurons (FSINs), making them a promising target for the regulation of drug-induced neuroplasticity. Brain regions within the circuitry of motivated

behavior with comparatively high PNN expression may provide neurobiological insight into maladaptive drug-induced neuroplasticity and subsequent drug seeking. Very little is known about how PNN-expressing neurons in the LHA control drug-seeking behavior. We previously reported that the dorsal and intermediate zones of the anterior lateral hypothalamic area (LHAad) exhibited robust PNN expression using the PNN marker *Wisteria floribunda* agglutinin (WFA), and that approximately two-thirds of WFA positive neurons co-expressed PV. Removal of PNNs with the enzyme chondroitinase ABC (Ch-ABC) expression blocked the acquisition of cocaine- but not sucrose-induced CPP and self-administration. Here we focused on the rodent model of relapse (reinstatement). The goals of this set of experiments were to: 1) determine whether PNN expression within the LHAad is necessary for cue-induced reinstatement 2) characterize the phenotype of LHAad PNN-surrounded neurons, and 3) determine mesocorticolimbic inputs to and projections from the LHAad. Here we report that LHAad PNNs are necessary for the expression of cue-induced reinstatement of cocaine-seeking behavior. Furthermore, the phenotype of LHAad PNN-surrounded neurons was determined using the excitatory markers VGLUT2 and glutamate and the inhibitory markers GAD65/67 and GABA. Predominant co-localization of WFA with VGLUT2 and GABA over GAD65/67 and glutamate suggests that the PNN-rich LHAad receives dense glutamatergic input (VGLUT2) and is predominantly GABAergic. Moreover, retrobead injection into the LHAad, NAc, and VTA demonstrates that the LHAad receives robust prefrontal cortex input while providing moderate input into the VTA and minimal input into the NAc. In summary, these data indicate that PNN expression in the LHAad: 1) is necessary for expression of cue-induced reinstatement of cocaine-seeking behavior 2) is predominantly co-localized with PV+ GABAergic neurons that receives robust glutamatergic inputs, and 3) receives input from layer V of the prefrontal cortex and provides input into the VTA.

Disclosures: **J.M. Blacktop:** None. **B.A. Sorg:** None.

Poster

704. Cocaine Seeking and Reinstatement I

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Title: Calcineurin regulates cocaine-cue neuroplastic changes in the amygdala to alter relapse-like behavior

Authors: *M. T. RICH[1,2], T. J. CAHANAP[2], Y. H. HUANG[2], M. M. TORREGROSSA[2]
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Abstract: Drugs of abuse induce neuroplastic changes within brain reward circuits, which create strong associative memories that can trigger drug-seeking behaviors. Disrupting these memories in individuals struggling with addiction may help maintain abstinence. The lateral amygdala (LA) is a key regulator of emotionally-salient memories, as it integrates thalamic and cortical input, including auditory and somatosensory information, to help guide behavior. Interfering with memory reconsolidation or inducing memory extinction within the LA may serve to weaken maladaptive memories. Extinction therapy, for example, has helped treat anxiety-based disorders, and has shown promise for preventing drug relapse. Previous studies have identified thalamic and/or cortical excitatory synapses within the LA as loci for cue-mediated learning. They are strengthened by associating a cue with a fearful or rewarding stimulus, and are weakened by fear-memory extinction. However, these mechanisms have not been well studied in the context of drug-associated learning. Extinction and reconsolidation are regulated by various protein kinases and phosphatases, such as CaMKII and calcineurin (CaN). Indeed, inhibiting CaMKII enhances the extinction of and interferes with the reconsolidation of drug-associated memories. To further investigate the synaptic mechanisms that regulate drug-cue memories, we utilized an approach that combined cocaine self-administration with *ex vivo* electrophysiology in male rats. We examined the effect of cocaine-cue learning at thalamic and cortical synapses in the LA, and whether these synapses were altered by cue extinction and reconsolidation. We then tested the behavioral and physiological effects of LA administration of chlorogenic acid (CGA), an activator of CaN. We found that cocaine training potentiated thalamo-amygdala but not cortico-amygdala synapses relative to saline-trained controls. This potentiation was unaltered by either instrumental extinction training or context exposure alone, and was not potentiated significantly more by reconsolidation. Alternatively, synaptic strength was progressively reduced by increasing levels of cue extinction. Finally, CGA infusions in the LA following extinction or reconsolidation significantly reduced both EPSC amplitude and cue-induced reinstatement relative to vehicle-infused controls. Together, our results suggest that inducing drug-cue memory extinction or inhibiting reconsolidation reverses cocaine-induced potentiation at thalamo-amygdala synapses in a CaN-dependent manner, and that this activity is important for reducing drug-seeking behavior.

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Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA15758

NIH Grant DA038663

Title: Mesolimbic endocannabinoid signaling involvement in chronic electric footshock stress-induced escalation of cocaine intake in rats

Authors: *J. R. MCREYNOLDS[1], C. P. WOLF[1], D. M. STARCK[1], R. SCHAPS[1], C. J. HILLARD[2], J. R. MANTSCH[1]
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Abstract: Stress is an important contributing factor to addiction and is problematic as stress is unavoidable in daily life. Addiction can be characterized by a loss of control over drug intake that, in the rat, is modeled by escalating patterns of drug self-administration (SA). We have previously shown that a stressor, electric footshock stress, administered daily at the time of SA induces an escalation of cocaine intake in rats that would otherwise demonstrate stable cocaine SA under short-access conditions (2-h/day). Stress-induced escalation of SA is likely the consequence of neuroplastic changes that may involve neurobiological mediators that connect stress-responsive and reward systems in the brain, such as the endocannabinoid system (eCB). These changes likely occur in regions implicated in both stress and reward, such as the nucleus accumbens shell (NAc) and ventral tegmental area (VTA). We hypothesize that repeated stress at the time of SA induces a persistent increase in eCB signaling, particularly in the NAc shell and VTA, which results in escalation of cocaine use and increased susceptibility to later reinstatement. Male SD were trained to SA cocaine (0.5 mg/kg/inf) on a FR 4 schedule in 4 X 30 min SA sessions separated by 5-min drug-free periods. Some rats received shock in the SA chamber during the 5 min drug-free period over 14 days. Shock administration resulted in an escalation of cocaine intake and this effect persisted for at least 5 days after cessation of shock. Systemic administration of the CB1R antagonist AM251 prior to the SA session attenuated cocaine intake only in stress-escalated rats. Surprisingly, intra-VTA administration of AM251 prior to the SA session attenuates cocaine intake regardless of stress condition. We are currently examining the effects of CB1R antagonism in the NAc shell on stress-induced escalation. Separate groups of rats were tested for reinstatement of drug-seeking behavior to a priming injection of cocaine (2.5, 5, or 10 mg/kg, i.p.). Rats who received shock during SA demonstrated augmented reinstatement to all doses of cocaine. Furthermore, as with SA, the CB1R antagonist AM251 given prior to injection of cocaine (10 mg/kg, ip) significantly attenuated cocaine-primed reinstatement only in stress-escalated rats. We are currently examining alterations in molecular components of the eCB system in stress- and reward-related brain regions. These data suggest that stress-induced neuroplastic changes occur, likely in the eCB system, in regions of the brain that influence expression of escalated cocaine intake and augmented cocaine-primed reinstatement and that these changes may be glucocorticoid-dependent.

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Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA15758

NIH Grant DA038663

Title: Sex differences in vulnerability to cocaine seeking are exaggerated by stress

Authors: *G. LIDDIARD[1], E. M. DONCHECK[1], M. C. DEBAKER[1], L. M. BARRON[1], C. D. KONRATH[1], J. R. MCREYNOLDS[1], E. N. GRAF[1], C. J. HILLARD[2], J. R. MANTSCH[1]
[1]Marquette Univ., Milwaukee, WI; [2]Med. Col. Wisconsin, Milwaukee, WI

Abstract: Female cocaine addicts display enhanced relapse vulnerability compared to their male counterparts, particularly during periods of stress. This phenomenon is poorly understood, and progress toward the identification of relapse-prevention targets has relied heavily on male-based investigations. Therefore, to pursue female-appropriate effective treatment targets, we investigated sex differences in stress-enhanced relapse vulnerability. Using the preclinical cocaine self-administration model, we previously found in males that under conditions where stress doesn't directly induce the reinstatement of drug seeking, it does augment reactivity to other triggers. Specifically, electric footshock stress (EFS; 0.2-msec, 0.5mAmp triplicate footshocks, 40-sec avg ITI, delivered randomly during a 15-min period prior to access to the previously cocaine-paired lever) and stress-response level corticosterone (CORT; 2 mg/kg, i.p., 40-min pretreatment) potentiate reinstatement in response to an ordinarily subthreshold dose of cocaine (2.5mg/kg, i.p.). To interrogate for sex differences in this phenomenon, we subjected gonadally-intact females to the same cocaine self-administration (0.5 mg/kg/0.2 mL i.v. infusion, 2-hr sessions x 14-days) and extinction conditions as the males. Despite equivalent, stable cocaine seeking during self-administration (avg active lever presses/session: 122.1 ± 0.9 males, 125.5 ± 2.1 females), and comparable extinction behavior (8-day avg to first extinction criterion for both sexes), females reinstated drug seeking to a cocaine dose that was subthreshold in males (2.5 mg/kg, i.p.). We next tested for CORT effects on a lower dose of cocaine (1.25 mg/kg, i.p.), which we found to be subthreshold for reinstatement in both sexes. While in females neither stress-level CORT nor 1.25 mg/kg cocaine alone were sufficient to produce reinstatement, pretreatment with CORT potentiated reinstatement to the ordinarily subthreshold 1.25 mg/kg cocaine. Significant reinstatement to 1.25 mg/kg cocaine was not observed in males, either alone or in concert with CORT. This suggests that females exhibit a lower threshold for cocaine-primed reinstatement, and that CORT potentiates reinstatement to ordinarily subthreshold cocaine doses in both sexes. This finding is consistent with clinical observations that females

exhibit enhanced relapse vulnerability compared to males, a difference exaggerated in the context of stress. Studies are underway to contrast the effects of EFS between males and females, and to determine whether the CORT dose that is physiologically-relevant in males is also physiologically relevant in females.

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Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

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NIH Grant DA038663

Title: The prelimbic cortical endocannabinoid system mediates stress-enhanced cocaine-seeking vulnerability: Investigation of sex differences

Authors: *E. M. DONCHECK[1], J. R. MCREYNOLDS[1], E. N. GRAF[1], O. VRANJKOVIC[1], M. C. DEBAKER[1], G. T. LIDDIARD[1], L. M. BARRON[1], C. D. KONRATH[1], L. A. URBANIK[1], Q.-S. LIU[2], C. J. HILLARD[2], J. R. MANTSCH[1]
[1]Biomed. Sci., Marquette Univ., Milwaukee, WI; [2]Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Relapse is provoked through distinct neurobiological mechanisms between subpopulations of cocaine addicts. Probing for individualized therapies is therefore more liable to identify effective relapse prophylactics. Key population differences emerge in the context of stress, as it only directly triggers relapse in a subset of addicts. Still, under conditions where stress cannot induce the reinstatement of cocaine seeking, we find that it can augment reactivity to other triggers. Following cocaine self-administration and extinction, neither stress-level corticosterone (CORT; 2 mg/kg) nor low-dose cocaine (2.5 mg/kg, i.p.) alone induce reinstatement, but do so in combination. This phenomenon occurs within the prelimbic cortex (PrL), as intra-PrL CORT (50 ng/side) is sufficient to potentiate reinstatement, an effect likely induced by CORT (100nM)-suppressed inhibition of PrL pyramidal neurons. Endocannabinoids (eCBs) mediate these effects, as intra-PrL cannabinoid receptor-1 (CB1) activation (AM251; 300 ng/side) and 2-arachidonoylglycerol synthesis (DO34; 0.1 & 1 µg/side) are necessary for potentiated reinstatement. Thus, we hypothesize that CORT-mobilized eCBs render PrL

projections more excitable by ordinarily subthreshold stimuli, resulting in greater reinstatement vulnerability.
However, these data were solely collected from males, and another key population difference emerges between the sexes. As females display enhanced relapse vulnerability, particularly during periods of stress, we tested for sex differences in CORT-potentiated reinstatement. Despite comparable drug seeking during self-administration (0.5 mg/kg/inf i.v., 2 hr/day *x* 14 days) and time to extinction criterion, females exhibit CORT-potentiated reinstatement to a lower subthreshold cocaine dose (1.25 mg/kg, i.p.) than males. Otherwise, intra-PrL CORT is sufficient, while intra-PrL CB1R activation is necessary, for potentiated reinstatement in females. Although such parallels suggest no sex difference in PrL eCB-mediated CORT-potentiated reinstatement, they do not explain the enhanced sensitivity observed in females. As females also exhibit relapse variability across the ovarian hormone cycle, testing is underway to correspond estrous phase to reinstatement responding. Our preliminary data indicate greater reinstatement when blood estrogen (E2) levels are elevated. Furthermore, we find that E2 (100nM) augments excitation of female PrL pyramidal neurons. Therefore, we hypothesize that E2 may complementarily interact with CORT-induced eCB-mediated disinhibition of PrL pyramidal neuron output to amplify relapse vulnerability in females.

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Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: DA038663

Title: Corticosterone potentiates reinstatement of cocaine seeking through activation of the cortico-accumbens pathway

Authors: *P. J. GOTTSHALL[1], J. R. MCREYNOLDS[1], T. STOLLENWERK[2], X. LIU[2], Q.-S. LIU[2], C. J. HILLARD[2], J. R. MANTSCH[1]
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Abstract: Stress not only can act as a powerful trigger for relapse to drug seeking, but it can potentiate responsiveness to other triggers for drug use. We have shown that under self-administration conditions where it does not reinstate cocaine-seeking, electric footshock stress

can potentiate reinstatement when paired with low-dose cocaine. This effect of shock is corticosterone (CORT)-dependent and is mimicked by systemic or intra-prelimbic cortex (PL) CORT administration, indicating that CORT is necessary and sufficient for stress-potentiated reinstatement and that the PL is a critical site of CORT action. CORT likely potentiates reinstatement through interactions with the endocannabinoid (eCB) system, as stress increases eCB production in the PL in a glucocorticoid-dependent manner. Supporting this, we have shown that systemic or intra-PL cannabinoid receptor 1 (CB1R) antagonism blocks stress- and CORT-potentiated reinstatement. Given that these CB1Rs are located primarily on GABAergic interneurons in the PL, CORT effects may be the result of eCB-mediated inhibition of GABA. Indeed, bath application of CORT to nucleus accumbens core-projecting neurons in PL slices attenuated inhibitory neurotransmission in a CB1R-dependent manner. Therefore, we hypothesize that this CB1R-dependent attenuation of inhibition in the PL leads to increased activation of pyramidal projection neurons, and increased output to the nucleus accumbens core (NAc), a pathway critical for reinstatement. Male SD rats self-administered cocaine (14 x 2-h/day) and then received an intra-NAc core injection of the retrograde tracer cholera toxin subunit B (CTb). Following recovery, rats underwent extinction training followed by reinstatement tests. Rats received an injection of CORT (2 mg/kg, i.p.) alone, subthreshold cocaine alone (2.5 mg/kg, i.p.) or both and were perfused after the reinstatement test. We utilized a double label immunohistochemical approach to determine CTb co-expression with an immediate early gene, cFos. Preliminary data indicates that CORT-potentiated reinstatement results in an increase in activation of the cortico-accumbens pathway. We are currently investigating the contribution of the eCB system to this effect and the behavioral relevance of this pathway to potentiated reinstatement utilizing an intersectional DREADD viral approach. These findings support the hypothesis that CORT acts in the PL, through CB1R-mediated inhibition of GABA, to potentiate reinstatement of cocaine seeking through increased activation of the cortico-accumbens pathway.

Disclosures: **P.J. Gottshall:** None. **J.R. McReynolds:** None. **T. Stollenwerk:** None. **X. Liu:** None. **Q. Liu:** None. **C.J. Hillard:** None. **J.R. Mantsch:** None.

Poster

704. Cocaine Seeking and Reinstatement I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 704.10/SS1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA033404

NIH Grant DA040965

Title: Perineuronal net removal decreases cue-induced reinstatement in cocaine self-administering rats

Authors: *J. WINGERT[1], R. P. TODD[2], B. A. SORG[3]
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Abstract: After the acquisition and consolidation of a memory, a memory trace can be made labile again by subsequent reactivation. Following reactivation, a memory trace undergoes a process called reconsolidation in which the memory trace must be stabilized if it is to persist. Reconsolidation can be initiated with the addition of a novel change from the preexisting memory trace. If the process of memory reconsolidation is disrupted by the activity of a drug or amnesic agent, the memory trace may be removed or left weakened. The medial prefrontal cortex (mPFC) is a key structure in processing rewarding stimuli and is important for cocaine-induced drug seeking behavior and memory. A subset of GABAergic interneurons within the mPFC expresses dense extracellular matrix structures called perineuronal nets (PNNs). Removal of PNNs with the enzyme chondroitinase-ABC (Ch-ABC) has been shown to induce a state of neural plasticity. We investigated the effects of Ch-ABC on the reconsolidation of a cocaine memory during a cocaine self-administration experiment. Male Sprague-Dawley rats were trained to lever press for cocaine on a fixed ratio 1 (FR1) schedule of reinforcement for 10 days. They were then given Ch-ABC or vehicle into their mPFC and, three days later, were given a 30-min memory reactivation session that used a variable ratio 5 (VR5) schedule instead of the FR1 schedule they were trained on. During the VR5, rats received both cocaine and the cocaine-associated cue light. The next day, rats were tested for memory reconsolidation by first measuring lever-pressing behavior for 30 min in the absence of the cue light (under extinction conditions) and for 30 min under cue-reinstatement conditions, in which rats were allowed to press for the cocaine-associated cue light. Injection of Ch-ABC into the mPFC did not change the response during the 30 min extinction session. However, rats given Ch-ABC decreased their response during the cue reinstatement session. Our results suggest that the removal of PNNs in the mPFC by Ch-ABC is effective at disrupting the reconsolidation of a cocaine-induced memory. The change in the self-administration paradigm (FR1 to VR5) may be required to make the memory labile for disruption by Ch-ABC.

Disclosures: J. Wingert: None. **R.P. Todd:** None. **B.A. Sorg:** None.

Poster

704. Cocaine Seeking and Reinstatement I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 704.11/SS2

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH DA033436

Title: Sex and estrous cycle effects on the attenuation of cue-primed reinstatement of cocaine-seeking by ceftriaxone

Authors: *P. HAMOR, A. R. BECHARD, M. SCHWENDT, L. A. KNACKSTEDT
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Abstract: Effective pharmacological treatments to prevent cocaine relapse remain elusive. Sex differences have been reported in human cocaine addicts for both intake and susceptibility to relapse; yet little is known about sex differences in pharmacological treatment of animal models of relapse. In male rats, the beta-lactam antibiotic ceftriaxone has consistently been demonstrated to reduce relapse to cocaine-seeking. Here, we assessed the ability of ceftriaxone to attenuate cue-primed reinstatement of cocaine-seeking in male and female rats. We also assessed the effects of estrous cycle on the ability of ceftriaxone to attenuate reinstatement in female rats. Male and female Sprague-Dawley rats self-administered cocaine (0.5 mg/kg per infusion) in the presence of discrete cues (light and tone) for 12 days (2h/day), followed by 2-3 weeks of extinction training of the operant response (lever presses). During the last week of extinction training, animals were treated with daily injections of ceftriaxone (200 mg/kg) or vehicle (saline), and then returned to the operant box for a cue-primed reinstatement test. We found that although female rats self-administered more cocaine across the 12 days, ceftriaxone attenuated cue-primed reinstatement of cocaine-seeking behavior similarly in both males and females. However, when reinstatement testing occurred during estrus, ceftriaxone did not attenuate cocaine-seeking. To investigate this effect further, we will use Western blot analyses to quantify proteins in the nucleus accumbens core that are known to be affected by ceftriaxone, such as xCT, GLT-1, GluA1, GluA2, mGlu5, an mGlu2/3. Our study is the first to confirm the ability of ceftriaxone to attenuate cue-primed reinstatement of cocaine-seeking behavior in females, dependent on estrous cycle. The current findings highlight the overall potential for ceftriaxone as a pharmacological treatment to prevent human cocaine relapse.

Disclosures: P. Hamor: None. **A.R. Bechard:** None. **M. Schwendt:** None. **L.A. Knackstedt:** None.

Poster

704. Cocaine Seeking and Reinstatement I

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Program#/Poster#: 704.12/SS3

Topic: G.08. Drugs of Abuse and Addiction

Support: P50 DA15369 (JFM)

R01 DA033579 (JFM)

F31 DA039709 (SMB)

F31 DA041021 (BMS)

Title: Chemogenetic inhibition of pyramidal neurons in prelimbic cortex blocks BDNF-mediated attenuation of cocaine seeking

Authors: *G. GIANNOTTI, S. M. BARRY, B. M. SIEMSEN, J. F. MCGINTY
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Abstract: A major clinical issue in addiction is the high rate of relapse even after prolonged abstinence. Our lab has shown that a single BDNF infusion into the prelimbic (PrL) cortex immediately after the last cocaine self-administration (SA) session attenuates reinstatement of cocaine-seeking. Moreover, inhibition of the TrkB receptor, ERK/MAPK activity, or AMPA/NMDA receptor function prevents BDNF's ability to attenuate relapse, indicating a relationship between BDNF-mediated suppression of cocaine-seeking and synaptic activation. Based on this evidence, we employed a chemogenetic approach to modulate glutamatergic activity in the PrL cortex by infusing an adeno-associated virus (AAV5, 0.75µL/side) carrying the cell type-specific promoter, CaMKIIα, to drive the expression of inhibitory $hM_4D(Gi)$ DREADD (Designer Receptors Exclusivity Activated by Designer Drugs) or eGFP in pyramidal neurons of the PrL cortex. Male rats were trained to self-administer cocaine (0.2 mg/infusion) for 14 consecutive days. Immediately after the last cocaine SA, all rats received an injection of clozapine-N-oxide (CNO, 10 mg/kg, I.P.) followed by an infusion into PrL cortex of PBS or BDNF 30 min later. Rats then underwent 6 days of abstinence followed by a post-abstinence test under extinction conditions, extinction training to criterion, a cue-induced reinstatement test, re-extinction, and a final cocaine prime-induced reinstatement test. As expected, infusion of BDNF in the eGFP-expressing rats attenuated relapse and activation of the Gi DREADD blocked BDNF's ability to attenuate cocaine seeking. It is important to note that 85% of mCherry neurons expressed CaMKIIα immunoreactivity. Surprisingly, the Gi DREADD, in the absence of BDNF, induced a long-lasting attenuation of relapse, raising the possibility that multiple brain regions receiving glutamatergic afferents from the PrL cortex contribute to subsequent relapse. To explore this possibility, we selectively inhibited glutamatergic activity in PrL neurons that project to the nucleus accumbens (NAc) core by infusing an AAV5 (0.75 µL/side) carrying a floxed form of the Gi DREADD into PrL cortex and a retrograde transducing CAV2-Cre virus (0.75 µL/side) into the NAc core of the same rats. As expected, infusion of BDNF in the eGFP-expressing rats attenuated relapse and CNO-mediated activation of the Gi DREADD blocked BDNF's ability to suppress cocaine seeking. However, activation of the Gi DREADD in the absence of BDNF did not affect relapse. Future experiments will explore the contribution of different brain regions receiving glutamatergic projection from the PrL cortex that may be involved in attenuation of relapse.

Disclosures: G. Giannotti: None. **S.M. Barry:** None. **B.M. Siemsen:** None. **J.F. McGinty:** None.

Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: P50 DA15369 (JFM)

R01 DA033579 (JFM)

T32 DA007288 (JFM)

F31 DA041021 (BMS)

Title: The effect of chemogenetic activation of the prelimbic cortex on relapse to cocaine-seeking: A potential role for glutamatergic pathway specificity

Authors: *B. M. SIEMSEN, G. GIANNOTTI, C. J. HU, J. A. MCFADDIN, J. F. MCGINTY
Med. Univ. of South Carolina, Charleston, SC

Abstract: Cocaine self-administration (SA) in rats transiently decreases phospho-ERK2, GluN2A/B- containing NMDA receptors, and activates striatal-enriched protein tyrosine phosphatase (STEP) within the prelimbic (PrL) cortex during early abstinence, suggesting a hypofrontal state. These neuroadaptations are critical for relapse to subsequent cocaine-seeking and are blocked by intra-PrL infusion of BDNF or the STEP inhibitor, TC-2153. Here we investigated the effect of activating the PrL cortex during early abstinence on relapse to cocaine-seeking using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). We hypothesized that chemogenetic activation of the PrL cortex immediately after the final SA session would prevent relapse to cocaine-seeking by normalizing the PrL cortical disturbance in phospho-proteins during early abstinence. Rats received chronic indwelling intravenous catheters followed by intra-PrL microinjections of an AAV5 encoding the excitatory DREADD hM3Dq driven by the CaMKIIα promoter (AAV5-CaMKIIα-hM3Dq-mCherry) or the control eGFP vector (UNC vector core, 0.75 µl/side; *n*=10/group), and were trained to self-administer cocaine (0.2 mg/infusion) for 12-14 days (2 hr/day) on an FR1 schedule of reinforcement. Immediately following the final session, rats were injected with CNO (3 mg/kg; i.p.) followed by 6 days of forced abstinence, a post-abstinence (PA) relapse test under extinction conditions, further extinction to criterion, a cue-induced reinstatement test, re-extinction, and a cocaine prime-induced reinstatement test. Contrary to our hypothesis, chemogenetic activation of the PrL cortex had a marginal effect on suppressing active lever pressing during the PA test and had no effect on cued or cocaine prime-induced reinstatement. This overall lack of effect on cocaine-seeking may be due to the recruitment of opposing projections arising from the PrL cortex, such that

activation of specific pathways may accentuate relapse, while simultaneous activation of alternative pathways may suppress relapse. In support of this hypothesis, preliminary data indicate that activation of the PrL cortex-nucleus accumbens core (NAc core) glutamatergic pathway during early abstinence using an intra-NAc core infusion of the retrogradely-transported CAV2-Cre in combination with an intra-PrL cortical floxed DREADD potentiates PA context-induced relapse and cue-induced reinstatement, but not cocaine prime-induced reinstatement. Future experiments will further dissect the effect of activating alternative pathways arising from the PrL cortex in cocaine-seeking after abstinence.

Disclosures: B.M. Siemsen: None. **G. Giannotti:** None. **C.J. Hu:** None. **J.A. McFaddin:** None. **J.F. McGinty:** None.

Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA037897

Title: Activation of amylin receptors in the nucleus accumbens reduces cocaine taking and seeking in rats

Authors: *Y. ZHANG, C. A. TURNER, H. D. SCHMIDT
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Abstract: Amylin is a peptide hormone co-secreted with insulin from pancreatic β-cells. Amylin crosses the blood brain barrier and activates amylin receptors expressed throughout the brain, including the mesolimbic dopamine system. Interestingly, there is a high density of amylin receptor binding sites in the nucleus accumbens (NAc), a brain region known to play a critical role in motivated behaviors. Central amylin signaling has been shown to regulate food intake. Specifically, activation of amylin receptors in the mesolimbic dopamine system has been shown to reduce the hedonic value of food. Given that the reinforcing effects of natural rewards and drugs of abuse are regulated by the mesolimbic dopamine system, these findings suggest that central amylin signaling may play an important role in addiction-like behaviors. The goal of these studies was to determine the role of amylin receptors expressed in the nucleus accumbens (NAc) shell and core in voluntary cocaine taking and the reinstatement of cocaine-seeking behavior. Using a within-subjects, counterbalanced design, amylin (0, 0.04, and 0.4 μg/μl) was administered directly into the NAc shell or core prior to self-administration and reinstatement test sessions. Our results show that intra-NAc shell amylin reduced cocaine self-administration under a fixed ratio 5 (FR5) schedule. In addition, amylin (0.4 μg/μl) in the NAc shell and core

attenuated cocaine reinstatement in rats. To determine whether the effects of amylin in the NAc generalize to other non-drug reinforced behaviors, separate groups of rats were used to study the role of central amylin receptors in operant responding for sucrose pellets. Our results indicate that administration of amylin directly into the NAc shell and core did not alter sucrose self-administration in either *ad libitum* fed or food-restricted rats. Taken together, these findings demonstrate an important role for central amylin receptors in preclinical models of cocaine addiction.

Disclosures: Y. Zhang: None. **C.A. Turner:** None. **H.D. Schmidt:** None.

Poster

704. Cocaine Seeking and Reinstatement I

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 704.15/SS6

Topic: G.08. Drugs of Abuse and Addiction

Title: Intermittent cocaine self-administration induces strong potentiation of incubation of cocaine craving in female rats

Authors: *C. NICOLAS, A. PIERCE, Y. SHAHAM, S. IKEMOTO
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Abstract: Cocaine seeking progressively increases during abstinence, a phenomenon termed 'incubation of cocaine craving'. Incubation of cocaine craving has been demonstrated after limited (2-h daily sessions) or extended access (6-h daily sessions) continuous cocaine self-administration. Recently, Zimmer et al. (NPP 2012) introduced an intermittent access self-administration procedure in which rats have access to cocaine for 5 min every 25 min during the daily sessions. They showed that this procedure increases the motivation to self-administration cocaine. Here, we studied whether intermittent cocaine self-administration will increase incubation of cocaine craving.
We first trained female rats to self-administer cocaine (0.75 mg/kg/infusion) continuously or intermittently for 12 days for 8-h/day, then assessed drug seeking in relapse tests after 2 or 29 abstinence days. During testing, lever presses were not reinforced with cocaine (extinction conditions). We found escalation of cocaine self-administration over 12-day drug sessions and higher non-reinforced lever presses after 29 abstinence days than after 2 days (incubation of cocaine craving) under both training conditions. More importantly, prior intermittent access cocaine self-administration led to significant increases in drug seeking on both day 2 and 29 and overall significant potentiation of incubation of cocaine craving (a significant interaction of access condition x abstinence day).
Our results extend previous reports showing that intermittent cocaine access increases the

motivation to seek cocaine by demonstrating that this training condition also causes potentiation of incubation of cocaine craving.

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Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA033049

NIDA Grant DA016511

Title: Oxytocin infused into the nucleus accumbens core decreases cocaine seeking and increases extracellular glutamate

Authors: C. N. LOGAN[1], R. WEBER[4], J. PERIS[2], K.-C. LEONG[5], L. A. KNACKSTEDT[3], *C. M. REICHEL[6]
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Abstract: Multiple neuropsychiatric disorders, including addiction, may benefit from oxytocin treatment. Oxytocin effectively reduces reinstated drug seeking in male and female rats. However, the underlying mechanisms of this effect have not been identified. It is well-established that glutamatergic synaptic transmission in the nucleus accumbens core (NAc) is dysregulated following cocaine self-administration. Here we suggest that oxytocin regulates activity of presynaptic glutamate terminals in the NAc. Male and female (Sprague-Dawley) rats self-administered cocaine, underwent extinction training, and were tested for cued cocaine seeking. During cued reinstatement, responses on the drug-associated lever resulted in a presentation of the light+tone stimulus complex originally associated with cocaine delivery. Before testing, rats received oxytocin or saline directly into the NAc or PFC. Some rats also received the mGlu2/3 receptor antagonist LY341495 or saline in the NAc before oxytocin. All rats readily acquired cocaine self-administration, and the majority met extinction criteria during the 8 extinction sessions. Oxytocin directly into the PFC did not impact lever responding for cocaine-conditioned cues relative to vehicle infusions. However, NAc oxytocin markedly decreased cued reinstatement and LY379268 in NAc reversed this effect. We hypothesize that oxytocin exerts these effects in the NAc through increases in extracellular glutamate levels thereby restoring tone on presynaptic glutamate terminals and decreasing cued reinstatement. To

begin to test this hypothesis, cocaine-naïve rats underwent reverse dialysis of 3.6 mM oxytocin in the NAc. The efflux was collected at 5 min intervals and glutamate content was quantified via HPLC. We detected a significant increase in extracellular glutamate following reverse dialysis of oxytocin. Together, our results show: 1) oxytocin increases NAc glutamate, 2) NAc oxytocin attenuates cued reinstatement, and 3) mGlu2/3 antagonism reverses oxytocin's effect. The precise mechanism by which oxytocin increased NAc glutamate is yet to be determined. One possibility is that oxytocin receptors on astrocytes in the NAc may increase astrocytic glutamate release through a Gq signaling mechanism to restore tone on presynaptic mGlu2/3 receptors. Another possibility is that oxytocin receptors may reside on presynaptic glutamate neurons in the NAc to directly regulate glutamate release. Future studies will target cell-type specificity of the oxytocin receptor to determine the source of increased glutamate and will determine whether NAc oxytocin increases glutamate in animals with a cocaine history.

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Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA/INSERM fellowship

Title: Opposite effects of BLA inactivation on context-induced relapse to cocaine seeking after suppression of drug self-administration by extinction versus punishment

Authors: *A. M. MINIER-TORIBIO, J. BOSSERT, Y. SHAHAM, Y. PELLOUX
Behavioral Neurosci. Br., NIH/NIDA/IRP, Baltimore, MD

Abstract: Background: Studies using the classical renewal procedure showed that basolateral amygdala (BLA) inactivation reduces context-induced relapse to cocaine seeking after extinction of the drug-reinforced responding. Here, we determined whether BLA inactivation would also inhibit context-induced relapse in a variation of the renewal procedure in which intermittent punishment suppresses drug-taking behavior, an animal model of human relapse after self-imposed abstinence due to adverse consequences of drug use. **Methods**: We trained rats to self-administer cocaine for 12 days for 6 h/day and then exposed them to either extinction or punishment training in context B (8 days). During punishment, 50% of cocaine-reinforced lever presses caused an aversive footshock; we increased the shock intensity daily by 0.1 mA from 0 mA to 0.7 mA. We then tested the rats for cocaine seeking in the absence of cocaine or shock in contexts A and B after BLA injections of vehicle or GABA agonists (muscimol+baclofen). Next,

we retrained the rats for cocaine self-administration in context A, reexposed them to the punishment or extinction conditions in context B, and retested for context-induced relapse after BLA vehicle or muscimol+baclofen injections. **Results**: BLA inactivation decreased context-induced relapse in context A after extinction in context B. In contrast, BLA inactivation increased context-induced relapse in context A after punishment in context B and provoked relapse in context B. **Conclusion**: Results demonstrate that BLA's role in drug relapse is critically dependent on the method used to achieve abstinence, highlighting the importance of studying drug relapse under abstinence conditions that more closely mimic the human condition.

Disclosures: A.M. Minier-Toribio: None. **J. Bossert:** None. **Y. Shaham:** None. **Y. Pelloux:** None.

Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH DA033436

Title: Pavlovian extinction and ceftriaxone differentially attenuate context- versus cue-primed cocaine relapse

Authors: *L. A. KNACKSTEDT, Y. PADOVAN HERNANDEZ, A. BECHARD
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Abstract: Relapse prevention is a significant challenge in the treatment of cocaine addiction, and no effective pharmacotherapies are currently available. Drug-associated cues maintain conditioned reinforcing properties that can trigger craving, leading to relapse. In human addicts, cue exposure therapy, which consists of repeated non-reinforced presentations of drug-associated cues, is used in an effort to reduce the association between cues and drug intake. Using an animal model, we sought to assess the effects of cue exposure therapy (Pavlovian extinction) in conjunction with ceftriaxone, an antibiotic that has previously been used to successfully attenuate relapse. Male Sprague-Dawley rats were trained to self-administer intravenous cocaine in the presence of discrete cues (light and tone). After 12 days of self-administration, rats entered a 3-week period of abstinence (remained in the home cage with daily handling). Half of the rats experienced Pavlovian extinction of drug-associated cues during the third week of abstinence (1h/day for 6 days). Rats were placed into a novel context and received 30 non-contingent presentations of the light and tone previously paired with cocaine delivery. During this time, rats were treated with ceftriaxone (200 mg/kg) or vehicle (saline). After 21 days of abstinence, rats underwent a context-primed test of relapse (no light or tone), and 24h later, a cue-primed test of

relapse. We found that, following Pavlovian extinction, ceftriaxone attenuated cue-primed relapse, but not context-primed relapse. To investigate the underlying circuitry involved in context- and cue-primed relapse after cue exposure therapy and how ceftriaxone interacts with this circuitry, in a separate group of rats we assessed the ability of ceftriaxone to reduce neuronal activation during cue vs. context primed relapse using cfos staining. Preliminary results suggest differential activation of brain regions involved in relapse induced by context versus discrete cues.

Disclosures: L.A. Knackstedt: None. **Y. Padovan Hernandez:** None. **A. Bechard:** None.

Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA032837

NIH Grant DA026582

Title: Tetrahydroisoquinoline orexin-1 receptor antagonists with improved drug-like properties

Authors: *Y. ZHANG, D. A. PERREY, A. M. DECKER, T. LANGSTON
Res. Triangle Inst., Research Triangle Park, NC

Abstract: Accumulating evidence has confirmed the involvement of the orexin system, particularly the orexin-1 (OX1) receptor, in different stages of the addiction of a variety of drugs. Blockade of the OX1R attenuated motivated drug seeking behaviors of cocaine, as well as ethanol and nicotine self-administration and reinstatement. We have recently reported a series of OX1 selective antagonists based on the tetrahydroisoquinoline scaffold, and in the process identified several structural features that enhance both potency and selectivity of OX1 over OX2. Here we describe the design and synthesis of a series of new analogs that incorporate these favorable structural features at multiple positions as well as structural alterations that may lead to improved physiochemical and pharmacokinetic properties.
All synthesized compounds were characterized by MS, NMR and HPLC, and then evaluated in calcium mobilization functional assays in RD-HGA16 (Molecular Devices) cell lines stably expressing either the OX1 or OX2 receptor. The structural alterations have resulted in tetrahydroisoquinoline derivatives showing potent and selective antagonism of OX1R, several of which had Ke < 10 nM. Moreover, efforts to improve the pharmacokinetic properties led to analogs with clogP values in the 3-4 range. These compounds showed much-improved aqueous solubility, good permeability, and modest half-life. These efforts will facilitate the development

of selective OX1 antagonists as therapeutics for drug addiction and other OX1 receptor mediated conditions.
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Disclosures: Y. Zhang: None. **D.A. Perrey:** None. **A.M. Decker:** None. **T. Langston:** None.

Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/NIDA DA033344

NIH/NIAAA AA024146

Title: Orexin A in the posterior paraventricular nucleus of the thalamus: promotion of reward seeking behavior and hypothalamic activation

Authors: *A. MATZEU[1], R. MARTIN-FARDON[2]
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Abstract: Orexin (Orx) neurons that arise from the dorsal hypothalamus and direct their signal to the paraventricular nucleus of the thalamus (PVT) have received growing interest as a part of reward circuitry. When injected in the posterior part of the PVT (pPVT), Orx-A reinstates (primes) cocaine-seeking behavior as well as a highly palatable food reinforcer after intermediate abstinence (Int-Abst). We previously reported that Orx-A administration in the PVT reinstated extinguished cocaine-seeking behavior in animals with short access (ShA) to cocaine (2 h/day) or long access (LgA) to cocaine (6 h/day; i.e., a model of cocaine dependence) as well as sweetened condensed milk (SCM) seeking. However, intra-PVT administration of Orx-A induced stronger reinstatement in the LgA group than in the ShA and SCM groups, which was associated with strong Fos activation and a significant increase in Orx^+/Fos^+ expression in the dorsomedial hypothalamus (DMH), perifornical area (PFA), and lateral hypothalamus (LH). Considering the long-lasting nature of drug-seeking behavior, the present study examined (1) whether the increase in Orx-A's priming effect endures after a longer period of abstinence and (2) whether this is associated with significant hypothalamic activation. Male Wistar rats were trained to self-administer cocaine ShA, cocaine LgA or SCM for 21 days. After training, the animals were subjected to protracted abstinence (Pro-Abst) that consisted of 14 days in the vivarium followed by extinction training for 14-21 days (2 h/day), during which the reinforcers were withheld. Once the animals' behavior was extinguished, they received intra-pPVT microinjections of Orx-A (0.5 µg) or vehicle and then were placed in operant chambers under

extinction conditions for 2 h. Immediately following the behavioral tests, the animals were euthanized, and their brains prepared for Fos and Orx immunolabeling in the LH, DMH, and PFA. In contrast to what was measured following Int-Abst, Orx-A did not reinstate cocaine-seeking behavior in the LgA group, but it exerted an augmented priming effect in the ShA and SCM groups, suggesting “incubation” of the priming effect of Orx-A in ShA and SCM animals but not in LgA animals. In parallel, strong brain activation (Fos^+ neurons) and a significant increase in Orx^+/Fos^+ expression were observed in the DMH, PFA, and LH in the SCM and ShA groups only. These data suggest that the functionality of Orx receptors and connectivity of the PVT□1DMH/PFA/LH circuit undergo significant neuroadaptation following Pro-Abst.
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Disclosures: **A. Matzeu:** None. **R. Martin-Fardon:** None.

Poster

704. Cocaine Seeking and Reinstatement I

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Title: Dynorphin counteracts orexin in the posterior paraventricular nucleus of the thalamus: cellular and behavioral evidence

Authors: *R. MARTIN-FARDON, M. KALLUPI, O. GEORGE, P. SCHWEITZER, A. MATZEU
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Abstract: The orexin (Orx) system is known to play a critical role in drug addiction and reward-related behaviors. The dynorphin (Dyn) system promotes depressive-like behavior and plays a key role in the aversive effects of stress. Both Orx and Dyn are co-released and have opposing functions in reward and motivation in the ventral tegmental area (VTA). Earlier studies from this laboratory showed that microinjections of OrxA in the posterior paraventricular nucleus of the thalamus (pPVT) exerted priming-like effects and reinstated cocaine-seeking behavior, suggesting that Orx transmission in the pPVT participates in cocaine-seeking behavior. The present study tested the hypothesis that Orx and Dyn interact in the pPVT and are involved in

controlling reward-seeking behavior. Using a cellular approach, brain slices from naive adult Wistar male rats were prepared for whole-cell recordings to study excitatory transmission in pPVT neurons. The superfusion of OrxA increased spontaneous glutamatergic transmission by increasing glutamate release onto pPVT neurons, whereas DynA decreased glutamate release. The augmentation of OrxA-induced glutamate release was reversed by DynA. To support the electrophysiological data, the influence of the OrxA-DynA interaction in the pPVT on seeking behavior was studied in animals that self-administered cocaine or a high palatable food reinforcer. Separate groups of male Wistar rats were trained to self-administer cocaine or sweetened condensed milk (SCM). After self-administration training, the rats underwent extinction training and then received intra-pPVT administration of OrxA±DynA under extinction conditions. OrxA reinstated cocaine- and SCM-seeking behavior, with a greater effect in cocaine animals. DynA selectively blocked OrxA-induced cocaine seeking *vs.* SCM seeking, whereas DynA alone did not exert any relevant behavioral effect in either group. These data indicate that DynA in the pPVT counteracts OrxA-induced cocaine seeking, perhaps by reversing the OrxA-induced increase in glutamate release, thus identifying a potential novel therapeutic target to prevent cocaine relapse.

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Poster

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Title: Glucagon-like peptide-1 receptor activation in the lateral dorsal tegmental nucleus attenuates cocaine seeking in rats

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Abstract: Cocaine addiction is a major public health concern for which there are no FDA-approved pharmacotherapies. Thus, new conceptual approaches to understanding the neurobiological basis of cocaine addiction are needed. Recent studies show that glucagon-like peptide-1 (GLP-1) receptor ligands reduce cocaine-mediated behaviors in rodents. GLP-1 is a

neuropeptide that is produced centrally in the nucleus tractus solitarius (NTS) of the caudal brainstem. However, no studies have examined the role of hindbrain GLP-1 receptors (GLP-1Rs) in the reinstatement of cocaine-seeking behavior, an animal model of relapse. Given that the lateral dorsal tegmental nucleus (LDTg): [1] plays a critical role in cocaine seeking, [2] expresses GLP-1Rs, and [3] receives direct projections from the NTS, the present study tested the hypothesis that GLP-1R signaling in the LDTg plays a critical role in cocaine seeking. Our preliminary data show that peripheral administration of the fluorescent GLP-1R agonist fluoro-exendin-4 (3.0 µg/kg i.p.) penetrates the brain, localizes in the LDTg and attenuates cocaine seeking. Therefore, we examined the effects of LDTg GLP-1R activation on cocaine reinstatement. Initially, rats were allowed to self-administer cocaine (0.25 mg/infusion i.v.) for 21 days on a fixed-ratio 5 schedule of reinforcement. Cocaine self-administration was then extinguished by replacing cocaine with saline. Once cocaine taking was extinguished, rats received an acute priming injection of cocaine (10 mg/kg i.p.) to reinstate drug-seeking behavior. During subsequent reinstatement test sessions, rats were pretreated with intra-LDTg infusions of the GLP-1R agonist exendin-4 (0, 0.005 and 0.025 µg) prior to a priming injection of cocaine. Here, we show that the 0.025 µg dose of exendin-4 attenuated cocaine priming-induced reinstatement. Parallel studies examining the effects of intra-LDTg exendin-4 on the reinstatement of sucrose seeking were conducted, which showed that 0.025 µg of intra-LDTg exendin-4 attenuated sucrose seeking. To assess the effects of cocaine self-administration and subsequent abstinence on endogenous central GLP-1 receptor signaling, LDTg GLP-1R and NTS preproglucagon (PPG; GLP-1 precursor) mRNA were collected following 1 day (Ext1) and 7 days (Ext7) of extinction. Using quantitative real-time PCR, we found that there were no changes in GLP-1R expression on Ext1 or Ext7 compared to yoked saline controls. However, we found a significant decrease in PPG expression levels on Ext7, which suggests a decrease in GLP-1 signaling in forebrain areas. Overall, these results highlight a novel role for hindbrain GLP-1R signaling in cocaine seeking.

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Poster

704. Cocaine Seeking and Reinstatement I

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Title: Nr4a2 in the medial habenula is a molecular regulator of cocaine reinstatement behaviors

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Abstract: The habenula complex is an epithalamic region composed of lateral and medial (MHb) substructures. Mounting evidence has demonstrated that the MHb is able to code for the aversive properties of nicotine, serving as a substrate for nicotine withdrawal and aversion through the dense expression of nicotinic acetylcholine receptors along the MHb-interpeduncular nucleus pathway. Although typically characterized as an “anti-reward” pathway, the endogenous function of the MHb has yet to be fully characterized. Moreover, the role of this pathway with regard to other drugs of abuse remains particularly unclear. Work from our lab and others has demonstrated that the MHb is engaged by reinstatement of cocaine-associated behaviors. Our initial studies demonstrated that chemogenetic activation of the cholinergic MHb population is able to induce reinstatement of cocaine-induced CPP. Yet, the molecular mechanisms within the MHb that are altered leading up, and in response, to reinstatement of cocaine behaviors are unknown. *Nr4a2*, a transcription factor critical in cocaine-associated behaviors and known regulator of dopaminergic signaling, is enriched in the cholinergic cell-population of the MHb. Furthermore, *Nr4a2* has been shown to be necessary for MHb development, but its role within the MHb in the adult brain remains elusive, specifically, given the lack of dopaminergic neurons within the MHb. We hypothesize that *Nr4a2* may mediate changes to the epigenome to changes in circuit function within the MHb to drive relapse-like behavior. Here, we seek to characterize the role of the Nr4a2 within the MHb in driving reinstatement of cocaine-induced CPP. To that end, we overexpressed Cre-dependent NR4A2, NURR2C (an endogenously-occurring, dominant-negative variant of NR4A2), or Empty Vector into the MHb of ChAT-Cre mice. Following viral delivery, animals underwent a previously described cocaine-primed CPP Reinstatement protocol to determine if NR4A2 within the MHb is necessary and sufficient for cocaine-reinstatement behaviors. As substance use disorders are a chronic relapsing disease, understanding the molecular and circuit mechanisms that regulate the relapse response will be critical in developing future therapies. This work seeks to identify a novel molecular regulator of MHb circuit function in a cocaine relapse-like behavior and will more completely characterize the role of MHb in drug-associated behaviors.

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Poster

704. Cocaine Seeking and Reinstatement I

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Title: A neural pathway mediating acupuncture effect on addiction: LHb-VTA/RMTg pathway

Authors: *S. CHANG[1], Y.-H. RYU[2], K. SONG[1], J. SHIN[1], M. KO[1], E. JANG[1], C. YANG[1], H. KIM[1]
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Abstract: Over the last four decades, public and scientific interest is increasing in acupuncture as an approach for treatment of drug addiction around the world We have shown that acupuncture activates endorphinergic input to mesolimbic dopaminergic (DA) system including VTA (Ventral Tegmental Area) or NAc (Nucleus Accumbens) to suppress the reduced DA levels in the NAc during ethanol abstinence, thereby reducing behavioral withdrawal signs. In addition, we have proposed a peripheral mechanism that the effects of acupuncture at HT7 on addiction are mediated by A-fiber activation of ulnar nerve at the wrist. However, the central pathway between peripheral acupuncture signals and mesolimbic reward circuit remains to be explored. Lateral habenula (LHb), a key epithalamic structure interconnecting sensory inputs to mesolimbic DA systems, is involved in processing of both peripheral sensory inputs (i.e., acupuncture) and reward and rostromedial tegmental nucleus (RMTg), the tail of VTA,mediates strong inhibitionof VTA activity and receives afferents neurons from the LHb. Based on these observations, we hypothesized that the LHb-RMTg circuit is involved in the inhibitory effects of acupuncture on addiction behaviors and DA release in NAc.
To test it, we examined(1) whether acupuncture stimulation inhibited cocaine-induced locomotor activity and the effects were blocked after lesioning LHb in rats, (2) the response of LHb activity following the acupuncture stimulation, (3) if an inhibitory effect by acupuncture on cocaine-induced both activation of NAc and DA release was affected by lesion of RMTg.
Bilateral lesions of either LHb or RMTg prevented the inhibitory effects of acupuncture

stimulation on the NAc neuronal activity and DA release following cocaine treatment. LHb neurons projecting to the VTA/RMTg regions, including GABAnergic neurons, were excited by acupuncture stimulation and LHb lesions reversed the acupuncture effects on cocaine locomotion. Taken together, these findings suggest that LHb-VTA/RMTg pathway is crucially involved in the acupuncture effect on the psychomotor response to cocaine.

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Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA042595

Title: Corticostriatal circuit representations of the incubation of cocaine craving in rats

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Abstract: Relapse to drug use is often preceded and accompanied by robust craving elicited by drug-paired cues and environments, and reports suggest drug craving or drug seeking progressively increases over a prolonged abstinence period. This “incubation” of drug seeking is linked to adaptations in brain circuits that are theorized to promote vulnerability to relapse. In particular, the nucleus accumbens (NAc) is a locus of convergence for motivationally relevant information from limbic and cortical (e.g., medial prefrontal cortex, mPFC) regions. However, the precise mechanisms of mPFC-NAc network encoding of cocaine cues and cocaine seeking in behaving animals are unknown. Simultaneous in vivo mPFC and NAc electrophysiological recordings demonstrate that incubation of craving is accompanied by amplified cue-evoked network oscillations in the mPFC and NAc as well as increased functional mPFC-NAc coherence. Importantly, cocaine seeking and these neural correlates are diminished following cell-type specific chemogenetic inactivation of mPFC to NAc projections. These findings suggest that progressive adaptations in the mPFC-NAc network may underlie cue-elicited cocaine craving and susceptibility to relapse after prolonged abstinence. These findings are likely to improve our potential to predict relapse vulnerability and to identify effective pharmacological and behavioral therapies.

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Poster

704. Cocaine Seeking and Reinstatement I

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Topic: G.08. Drugs of Abuse and Addiction

Support: R01 DA034684

Title: Activity-guided inhibition of the infralimbic cortex reveals a critical temporal window in the extinction of cue-driven cocaine seeking

Authors: *K. NETT[1], A. L. GUTMAN[1], R. T. LALUMIERE[2]
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Abstract: Prior evidence indicates that the medial prefrontal cortex regulates cocaine-seeking behavior. In particular, studies suggest that the ventral portion of this region, known as the infralimbic cortex (IL), mediates the inhibition of cocaine seeking. However, the precise temporal relationship among IL activity, lever pressing, and the extinction of cocaine seeking remains unclear. To address this issue, we used an activity-guided "closed-loop" optogenetic approach in which IL activity was silenced during specific periods of reinstatement testing. Male Sprague-Dawley rats received bilateral injections of AAV-CaMKIIα-eArchT3.0 into the IL and bilateral fiber optic probes aimed at the IL. They then underwent two weeks of daily 2 h cocaine self-administration sessions, in which active lever presses produced a cocaine infusion (200 μg/infusion), light/tone cues, and retraction of the lever for 20 s. Following this, rats underwent extinction training, in which active lever presses yielded no cocaine or cues but still led to lever retraction, prior to initiating reinstatement testing (cued and cocaine-primed). During reinstatement, active lever presses resulted in a 20 s lever retraction and bilateral illumination of the IL for 20 s to produce temporally restricted inhibition of IL activity. Each rat underwent reinstatement twice, receiving illumination or no light (sham-control) in a counterbalanced manner, with re-extinction between each reinstatement. The results indicate that IL inhibition after a lever press significantly increased active lever pressing during the cued reinstatement session, suggesting that the inhibition disrupted the within-session cued extinction encoding. In contrast, IL inhibition after each lever press during a cocaine-primed reinstatement had no effect on lever pressing during the session. Finally, to determine whether the post-lever press period was critical for the within-session extinction encoding during cued reinstatement, a separate cohort of rats underwent cued reinstatement but received the 20 s bouts of IL inhibition in a pseudo-random manner that was unrelated to the lever pressing. In this case, inhibition had no effect on active lever presses during the session. These findings suggest that the 20 s period following a lever press during cue-driven cocaine seeking reflects a critical window during

which IL activity encodes the new contingencies between the cues and lack of a cocaine reinforcer.

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Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Title: Limbic projections to the claustrum in the rhesus monkey (Macaca mulatta)

Authors: *J. T. JACOBS, M. GORSICH, M. MISHKIN, R. C. SAUNDERS
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Abstract: The claustrum is a subcortical grey matter structure situated lateral to the striatum and medial to the insula within the primate brain. Little is known about its function, with theories ranging from sensory integration to direction of attentional resources. Though many studies have confirmed claustral connectivity with all sensory cortical areas, relatively little is known about its connectivity with limbic regions. A better understanding of limbic projections to the claustrum might provide insight into its function. To examine limbic inputs into the claustrum we injected retrograde tracers into various dorsal-ventral (DV) and rostral-caudal (RC) locations within the claustrum. We also injected anterograde tracers into several limbic areas (amygadala, cingulate cortex, and rhinal cortex) to confirm and extend the findings of the retrograde injections. Retrograde labeled cells were found in all limbic regions except for the hippocampus. Cingulate area 24 displayed dense labeling in deep and superficial layers after rostral injections, and moderate labeling after caudal injections. In contrast, there were fewer labeled cells in area 25. In all cases enthorhinal cortex, area 28, exhibited a moderate degree of labeling limited to deep layers. Areas 35 and 36 of the perirhinal cortex had a greater density of labeled cells in both the deep and superficial layers. In the amygdala, labeling was generally denser following ventral injections, however the lateral basal nucleus showed dense labeling in all cases. Moderate to dense labeling was present in the accessory basal, central, and medial nuclei after rostral to mid-RC injections, while caudal injections resulted scarcer label. In contrast, the lateral nucleus had a moderate to high degree of labeling after injections into the mid-RC to caudal claustrum, but not after rostral injections. The hippocampus did not exhibit labeling in any of the retrograde cases. Cortical anterograde tracer injections supported the retrograde findings. Cingulate injections resulted in moderate labeling throughout the claustrum, especially in the mid-DV to ventral regions with the density of label decreasing in caudal sections. After injections into the perirhinal cortex labeling was moderate in caudal sections and limited to the ventral region. Entorhinal injections resulted in labeling of the mid-DV to ventral claustrum predominantly at the mid-RC

to rostral levels. Amygdala injections led to a moderate amount of labeling, mainly in the caudal ventral claustrum but also in the mid-DV claustrum. These findings suggest that the claustrum serves as a point of convergence for both sensory and limbic information.

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Poster

705. Cortical and Thalamic Circuits

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Topic: H.01. Animal Cognition and Behavior

Support: UW2020

Title: Functional and metabolic connectivity of the awake and anesthetized primate brain

Authors: A. B. MCMILLAN[1], A. Z. RAJALA[2], S. A. HURLEY[2], B. J. STIEVE[2], R. L. JENISON[3], R. M. BIRN[4], *L. C. POPULIN[2]
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Abstract: Functional connectivity, correlated fluctuations of the BOLD signal, is thought to reflect an evolutionarily conserved aspect of the functional organization of the brain, as they are observed under awake and anesthetized conditions. As a fundamental measure of brain organization that, as postulated, transcends levels of consciousness, it should remain unaltered under different physiological states. We tested this hypothesis directly using Rhesus monkeys imaged awake and anesthetized within the same sessions.
Because most of the energy consumed by the brain is used to maintain essential metabolic processes, i.e., the basic functional organization of the brain, we simultaneously measured metabolic activity using 18F-FDG along with the BOLD signal. We hypothesized that both measures should remain unaltered by the administration of ketamine (Ket).
Three monkeys were trained to sit quietly during imaging. Four 13.5 min runs of PET/MR data were obtained; the 1st and 2nd under awake conditions, and the 3rd and 4th after injection of 4 and 2 mg/kg of Ket (IV), respectively. Imaging was performed on a GE 3T Signa PET/MR scanner. fMRI parameters were: 1.8s TR, 20.5ms TE. During fMRI, 18F-FDG was infused at a rate of 0.01 mL/s (~3.5 mCi/scan). Data analysis for fMRI used a seed-based approach with field-map correction, motion correction, bandpass filtering, and smoothing. PET was reconstructed from list mode data with 30s frame duration using an iterative, time-of-flight reconstruction. Dynamic PET (dPET) data were processed like the fMRI data (motion correction, global brain signal, and smoothing). Seed-based resting connectivity correlation analysis was

performed in both fMRI and dPET data to identify networks. Effective connectivity between regions was assessed using time-domain conditional Granger causality (CGC) based on a state-space model. The magnitude of each conditional pair-wise CGC between network nodes was tested using nonparametric permutation tests corrected for multiple hypotheses.
Both fMRI and dPET analysis identified a similar fronto-parietal network (FPN). CGC analyses demonstrated significant directional flow between brain regions (nodes) of the FPN in the awake state. Administration of Ket produced a large and significant disruption in fMRI, dPET, and CGC connectivity measures, indicating that these networks are not maintained across different physiological states.

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Poster

705. Cortical and Thalamic Circuits

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Title: Innervation differences of layer 5a and 5b Martinotti cells in frontal cortex

Authors: *Y. KAWAGUCHI, M. MORISHIMA
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Abstract: Martinotti cells (MCs) are one of the major GABAergic cell subtypes in the neocortex, and express somatostatin. Their ascending axons innervate mainly dendrites of pyramidal cells. In layer 5 (L5), some somatostatin MCs exhibit calcium-dependent low-threshold spikes (LTS-MCs). In the rat frontal cortex, L5 is composed of the upper (L5a) and lower (L5b) sublayers. L5b receives more robust input from thalamocortical fibers than L5a. The major subtype of L5 PCs is corticopontine (CPn) cells that project to the striatum of basal ganglia and the pontine nuclei innervating the cerebellum. CPn cells in L5a more preferentially send their axons to other cortical areas than L5b, whereas L5b CPn cells more to the spinal cord. These suggest that their inhibitions from Martinotti cells may be also different within the L5 sublayers. Therefore, we compared the connections with CPn cells and axonal arborization of L5a and L5b LTS-MCs, using in vitro whole cell recording and morphological reconstruction of recorded cells in rat frontal cortex. Both L5a and L5b CPn cells were innervated by LTS-MCs,

and IPSC amplitudes were similar between the sublayers. However, the reciprocal connections were more found in L5a than L5b. LTS-MC axon densities in layer 1 (L1), another thalamocortical-recipient zone, preferentially arose from L5a LTS-MCs. The spatial overlap of CPn cell dendrites and LTS-MC axons suggest that L5a LTS-MCs innervate not only basal and apical oblique dendrites of CPn cells, but also their dendritic tufts within L1. On the other hand, L5b LTS-MC axons target more selectively the basal and oblique dendrites of CPn cells. These results suggest that LTS-MCs innervating CPn cells are further differentiated according to the L5 sublayers and L1 innervation pattern, related to the thalamocortical inputs. Supported by grants: KAKENHI 25250005, 15K14324, 17H05589 from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Poster

705. Cortical and Thalamic Circuits

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South African National Research Foundation

Title: Comparative morphology of gigantopyramidal neurons in primary motor cortex across mammals

Authors: *B. G. JACOBS[1], M. E. GARCIA[1], N. B. SHEA-SHUMSKY[1], M. TENNISON[1], L. J. SLOAN[1], A. P. WARLING[1], M. SCHALL[1], A. J. BULL[2], M. RAGHANTI[3], A. H. LEWANDOWSKI[4], B. WICINSKI[5], H. CHUI[1], M. F. BERTELSEN[6], T. WALSH[7], A. BHAGWANDIN[8], M. A. SPOCTER[9], P. R. HOF[5], C. C. SHERWOOD[10], P. R. MANGER[8]
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Abstract: Gigantopyramidal neurons, referred to as Betz cells in primates, were first identified in the primary motor cortex by Betz in 1874 and are characterized by large somata and extensive

basilar dendrites (Lewis, 1878). Although there have been morphological descriptions and drawings of gigantopyramidal neurons in a limited number of species, quantitative analyses have typically been limited to measures of soma size. The current study thus quantitatively investigated gigantopyramidal neurons in the primary motor cortex of 19 species across eight taxa: feliforms (caracal, clouded leopard, lion, mongoose, Siberian tiger), primates (baboon, golden tamarin, human, lemur), artiodactyls (blue wildebeest, giraffe, kudu), caniforms (African wild dog, domestic dog), perissodactyls (mountain zebra, plains zebra), a diprotodont marsupial (wallaby), a lagomorph (rabbit), and a murid rodent (rat). Of the 617 neurons traced, 181 were gigantopyramidal neurons; for comparative purposes, deep pyramidal (n = 203) and superficial pyramidal (n = 233) neurons were also quantified. Gigantopyramidal neurons were not identified in the wallaby, mongoose, rabbit, or rat. Qualitatively, dendritic morphology varied considerably across taxa, with both perissodactyls and artiodactyls exhibiting widely bifurcating, V-shaped apical dendrites. Quantitatively, most dendritic measures were significantly greater in gigantopyramidal neurons than in superficial and deep pyramidal neurons. Cluster analyses of dependent measures revealed that most taxa could generally be discriminated with a high degree of accuracy for both superficial and gigantopyramidal neurons. Finally, in agreement with Brodmann (1909), gigantopyramidal neurons were particularly large in feliforms, presumably due to specializations in muscle fibers and muscle coordination in this taxon.

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Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 705.05/SS22

Topic: G.07. Other Psychiatric Disorders

Title: Utilizing 24(S)-hydroxycholesterol to identify patient populations and clinical endpoints: Negative emotion processing in Huntington's disease as proof of principle

Authors: *M. C. LEWIS[1], J. DAI[1], J. KENNEDY[1], B. BOROWSKI[2], A. MOHAN[2], S. TABRIZI[3], A. ROBICHAUD[1], J. DOHERTY[1], M. QUIRK[1]
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Abstract: 24(S)-hydroxycholesterol (24(S)-HC) is an endogenous, brain specific, cholesterol metabolite that acts as a positive allosteric modulator of the N-methyl-D-aspartate (NMDA)

receptor. Alterations in plasma and/or brain levels of 24(S)-HC have been identified in several diseases, including Smith-Lemli-Opitz syndrome, Niemann Pick, Huntington's disease (HD), and some forms of dementia. Although a broad range of pathology and core symptomology is observed across these different disorders, all manifest some degree of behavioral and psychiatric symptoms. One important question to be addressed is whether 24(S)-HC is associated with these symptoms and, if so, which features are most directly associated with decreased glutamatergic tone. Cognitive deficits are a hallmark of HD, and can precede the onset of motor impairments by decades. One of the most consistent cognitive findings in HD are deficits in emotional face processing, which are present in both manifest and pre-manifest HD. Previous work has established that levels of 24(S)-HC are decreased in plasma and brain in HD patients, suggestive of decreased NMDA receptor function. Here, we investigated the relationship between 24(S)-HC and emotional face processing in samples from TRACK-HD, a longitudinal biomarker study of pre-manifest and early stage HD. Plasma samples from the TRACK-HD study (60 control; 60 Pre-HD; 60 HD) were analyzed for 24(S)-HC via liquid-liquid extraction and analyzed with LC-MS/MS. Regression analysis was then performed between oxysterol levels and performance on the Ekman and Friesen emotion recognition task. We find that 24(S)-HC levels are positively correlated with performance on an emotional face processing task that is not due to overall neurodegenerative processes. Importantly, we found no relationship between emotional face processing and other oxysterols (25- and 27-HC) suggesting a specific role for central nervous system derived 24(S)-HC. These data support a critical role for NMDA receptor function in negative emotion processing in HD, and identify emotion recognition as a potential clinical endpoint.

Disclosures: **M.C. Lewis:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **J. Dai:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **J. Kennedy:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **B. Borowski:** None. **A. Mohan:** None. **S. Tabrizi:** None. **A. Robichaud:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **J. Doherty:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **M. Quirk:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics.

Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 705.06/SS23

Topic: G.07. Other Psychiatric Disorders

Title: A pharmacological characterization of novel oxysterol modulators of nmda receptors

Authors: *M. A. ACKLEY, A. ALTHAUS, M. C. QUIRK, G. MARTINEZ-BOTELLA, F. G. SALITURO, A. J. ROBICHAUD, J. J. DOHERTY
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Abstract: NMDA receptors (NMDA-R) are intimately involved in neuroplasticity and network activity of neuronal circuits and as such, represent targets of interest for drug development for CNS diseases. Positive modulators of NMDA-R are in development for their potential to alleviate cognitive deficits in diseases such as schizophrenia and dementia as well as in other areas of demonstrated NMDA hypofunction such as anti-NMDA encephalitis and neurodevelopmental disorders. We recently reported that the endogenous oxysterol, 24(S)-hydroxycholesterol (24(S)-HC) directly modulates the NMDA-R and positively impacts plasticity in the hippocampus (Paul *et al*, 2013). Subsequently, we have developed synthetic positive modulators of NMDA-R and two prototypical compounds demonstrated here are SGE-301 and SGE-550. We have previously characterized the electrophysiological properties of these novel positive allosteric modulators in heterologous cell lines expressing human NMDA-R in multiple electrophysiology platforms. Here we further characterize the subunit selectivity and demonstrate that SGE-550 displayed broad activity across all subunit combinations, whilst SGE-301 lacked activity at GluN2C subunits. We have also undertaken a series of mechanistic experiments to show a differential response for how these compounds affect glutamate, glycine and d-serine concentration-response curves at NMDA-R. For example, both SGE-301 and SGE-550 shifted the Glutamate and Glycine concentration-response curves to the left, so that the agonist appeared more potent. Both compounds increased the maximum current response to glutamate, but not to glycine. To understand the interaction of SGE-301 and the endogenous oxysterol, 24(S)-HC, we ran an occlusion experiment. In the presence of ascending concentrations of 24(S)-HC, the concentration response to SGE-301 was shifted to the right suggesting a competitive interaction at the putative oxysterol site on the receptor. Although we believe this oxysterol binding site to be distinct from the agonist sites, we chose to see if oxysterols could overcome the effect of competitive inhibitors at these sites. L-Phenyalanine has been shown to inhibit NMDA-R by acting as a glycine site antagonist. We confirmed that L-Phenylalanine inhibited NMDA-R and we could overcome this inhibition using SGE-550. Finally, oxysterols enhanced evoked NMDA post synaptic potentials in brain slices, confirming

their activity at native NMDA-R. The data presented further characterize the pharmacology of compounds the oxysterol class of NMDA-R modulators.

Disclosures: **M.A. Ackley:** A. Employment/Salary (full or part-time):; SAGE Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SAGE Therapeutics. **A. Althaus:** A. Employment/Salary (full or part-time):; SAGE Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SAGE Therapeutics. **M.C. Quirk:** A. Employment/Salary (full or part-time):; SAGE Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SAGE Therapeutics. **G. Martinez-Botella:** A. Employment/Salary (full or part-time):; SAGE Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SAGE Therapeutics. **F.G. Salituro:** A. Employment/Salary (full or part-time):; SAGE Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SAGE Therapeutics. **A.J. Robichaud:** A. Employment/Salary (full or part-time):; SAGE Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SAGE Therapeutics. **J.J. Doherty:** A. Employment/Salary (full or part-time):; SAGE Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SAGE Therapeutics.

Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 705.07/SS24

Topic: G.07. Other Psychiatric Disorders

Title: Novel oxysterol NMDA receptor positive allosteric modulators exhibit diverse effects in an *In vitro* model of cortical network activity

Authors: *A. L. ALTHAUS, M. ACKLEY, M. QUIRK, G. MARTINEZ BOTELLA, F. SALITURO, A. ROBICHAUD, J. DOHERTY
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Abstract: 24(S)-hydroxycholesterol (24(S)-HC) is a potent endogenous NMDA receptor positive allosteric modulator (PAM). The NMDA receptor plays a critical role in neuronal excitability and plasticity. As a result, compounds that positively modulate current through the NMDA receptor might have therapeutic utility in conditions that are associated with NMDA receptor hypofunction. Synthetic analogues of 24(S)-HC retain and expand the PAM activity at

the NMDA receptor and display a range of potency and Emax across different NMDA receptor subtypes in vitro. We profiled oxysterol-based NMDA receptor modulators, in an *in vitro* model of cortical network activity in order to understand the impact of enhancing NMDA receptor function on spontaneous neuronal activity.
We compared 24(S)-HC with a series of novel synthetic analogues that displayed a range of modulatory activity at NMDA receptors. Mouse primary cortical neurons were cultured on multielectrode array plates and network activity was measured after 27 days in vitro (DIV) with the Plexon system by NeuroProof (Rostock, Germany). The baseline activity profile of each culture (N = 10 per compound) was recorded for one hour followed by the administration of eight cumulatively increasing concentrations of the test compound. Network activity was assessed for one hour per concentration and the results were normalized to the culture's own baseline activity.
24(S)-HC produced a significant, concentration-dependent increase in network activity as measured by spike rate, with an EC_{50} of 146nM. Most synthetic analogues also significantly increased spike rate with similar or greater potency. Interestingly, some of the compounds did not significantly increase spike rate of the network, despite their NMDA receptor PAM activity in heterologous cells. Indeed, a minority of the compounds tested even significantly reduced spike rate at some concentrations. The compounds also differentially affected network oscillatory activity and synchrony.
We found that oxysterol-based NMDA receptor PAMs can alter spontaneous cortical network activity in vitro in a concentration-dependent fashion. Though all compounds tested had NMDA receptor PAM activity, effects on network activity were complex, with some compounds increasing spike rate, burst firing, and synchronous activity, whereas others decreased or did not affect these parameters.. Ongoing work aims to elucidate the mechanistic differences observed with NMDA PAMs in these in vitro cortical networks.

Disclosures: **A.L. Althaus:** A. Employment/Salary (full or part-time):; Sage Therapeutics. **M. Ackley:** A. Employment/Salary (full or part-time):; Sage Therapeutics. **M. Quirk:** A. Employment/Salary (full or part-time):; Sage Therapeutics. **G. Martinez Botella:** A. Employment/Salary (full or part-time):; Sage Therapeutics. **F. Salituro:** A. Employment/Salary (full or part-time):; Sage Therapeutics. **A. Robichaud:** A. Employment/Salary (full or part-time):; Sage Therapeutics. **J. Doherty:** A. Employment/Salary (full or part-time):; Sage Therapeutics.

Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 705.08/SS25

Topic: H.01. Animal Cognition and Behavior

Support: NRF 2014R1A1A2057042

KHIDI HI17C0368

Title: Cognitive interaction between territorial infarction and chronic cerebral hypoperfusion in a rat model

Authors: D. BACK, *H. KIM
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Abstract: Background: Poststroke dementia (PSD) is one of main consequences after ischemic stroke. Ischemic stroke is accompanied by secondary neurodegenerative with upregulation of β amyloid precursor protein (APP) and amyloid β (Aβ) deposits localized to the ischemic core and surrounding penumbra. After territorial infarction, some patients develop PSD and some do not. To elucidate this unresolved question, chronic cerebral hypoperfusion (CCH) as a frequent consequence of cerebrovascular dysfunction has considered as the major cause for exacerbating the development of dementia following ischemic stroke.
Methods: The adverse effects of CCH on a neurodegenerative status which deteriorate cognitive functions in the course of post stroke were investigated by a novel animal model. Primarily, the right middle cerebral artery was transiently occluded (tMCAo) for 90 min in Wistar rats to mimic focal cerebral ischemia clinically, yielding territorial infarction which triggered the accumulation of Aβ aggregates. After 2 week, tMCAo rat models were subjects to permanent occlusion of bilateral common carotid arteries (BCCAo) for 6 weeks to mimic CCH mechanism. In addition to tMCAo + BCCAo models, three types of models were added to be compared: sham + sham operated rats; tMCAo + sham operated rats; and sham + BCCAo operated rats. Spatial memory, motor, perception and cognition functions were assessed in Morris water maze test, modified neurological severity score test, foot fault test, and parallel bar test. To evaluate the degree to which either ischemia or CCH, or both of them affected neurodegeneration, various antibodies for immunoreactivity in the rat brain including the cortex, hippocampus, striatum, thalamus, and penumbra were used as follows: Aβ, APP, tau, ionized calcium binding adaptor molecule 1, glial fibrillary acidic protein, NeuN, and microtubule associated protein 2.
Results: Compared to the other three types of rat models, tMCAo + BCCAo group showed considerable spatial memory impairment. Interestingly, BCCAo group representing the effect of CCH revealed more memory decline than tMCAo group. As a result, CCH may be an aggravating factor to acute territorial infarction, potentially bringing PSD. Immunohistochemical analysis may also suggest that the aggravation in aggregated Aβ, tau, inflammatory responses and neuronal loss in tMCAO + BCCAo models explaining PSD mechanism.
Conclusion: tMCAo + BCCAo model provided a novel insight into how CCH has a deleterious effect on the development of PSD after acute territorial infarction. CCH may be the major aggravating factor to develope cognitive dysfunction after territorial infarction, leading to PSD.

Disclosures: D. Back: None. **H. Kim:** None.

Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 705.09/SS26

Topic: H.01. Animal Cognition and Behavior

Support: MOE2015-T2-2-095

Title: Functional classification of claustrum neurons

Authors: *M. GRAF, G. J. AUGUSTINE
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Abstract: We characterized the intrinsic electrical properties of neurons within the claustrum, a poorly-understood structure that is the most highly interconnected part of the brain (Human Brain Mapping 36: 827). Whole-cell patch-clamp recordings in acute brain slices were used to determine neuronal intrinsic properties based on responses to depolarizing current pulses at current levels twice action potential (AP) threshold, to side-step differences in cell input resistance. Based on recordings from more than 350 neurons, several parameters were correlated with at least one other parameter: (1) amount of AP frequency adaptation, (2) ratio of first-to-last interspike intervals, (3) amplitude of AP after-hyperpolarization (AHP), (4) rate of AP repolarization; and (5) ratio of rates of AP rise/decay. Based on the correlations between these parameters, the data were clustered pairwise in an unsupervised manner (ClustVis software) to define specific cell types. This analysis revealed that claustrum neurons can be grouped into 2 main populations, depending on whether they show strong (SA) or mild (MA) AP frequency adaptation. SA cells also had smaller AHP amplitudes compared to MA cells and were further subdivided into at least 2 subgroups based on other differences in their intrinsic properties. One SA subgroup exhibited the highest amount of adaptation, as well as small AHP amplitudes and a tendency to fire 2 or 3 APs at the beginning of a depolarization. The second SA subgroup had a rate of AP repolarization that was slower than for the other SA cells. Post-hoc immunostaining revealed that all SA neurons are glutamatergic projection neurons because they expressed tbr1, a marker for projection neurons. MA neurons were more heterogeneous and typically expressed either tbr1 or interneuron markers, such as parvalbumin, somatostatin, or VIP. Thus, MA neurons include both projection neurons and interneurons. Both groups of MA cells also showed differences in their intrinsic properties: interneurons usually had larger AHPs, a faster rate of AP repolarization and a smaller ratio of AP rise/decay than MA projection neurons. In summary, our results indicate that the diverse array of neurons found in the claustrum can be classified according to their intrinsic electrophysiological characteristics. This information will facilitate future efforts to characterize claustrum neuron function and network dynamics.

Disclosures: M. Graf: None. **G.J. Augustine:** None.

Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

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Program#/Poster#: 705.10/SS27

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1T32 NS086750

NIH Grant R01 MH085974

Title: Reciprocal circuits linking the prefrontal cortex and thalamus

Authors: *D. COLLINS, P. ANASTASIADES, J. MARLIN, A. CARTER
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Abstract: Bidirectional communication between the prefrontal cortex (PFC) and thalamus is critical for cognition and attention. However, the cell-type and pathway-specific circuits that link these two brain regions remain poorly understood. Here we use optogenetics, whole-cell physiology and 2-photon microscopy to study cortico-thalamo-cortical loops in the mouse brain. We first study connections from the PFC onto relay neurons in the thalamus. We then examine synapses from the thalamus onto cortico-thalamic neurons in the PFC. Finally, we examine the properties of thalamic inputs onto other subpopulations of projections neurons within the PFC. Together, our findings reveal open and closed feedback loops involved in multiple PFC and thalamic circuits.

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Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 705.11/SS28

Topic: H.01. Animal Cognition and Behavior

Title: Motor cortical control of thalamus projecting inhibitory neurons in the brainstem

Authors: *V. M. PLATTNER[1], E. BőSZ[1], M. A. DIANA[2], L. ACSÁDY[1]
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Abstract: Our previous data demonstrated that glycine transporter2 (GlyT2) positive inhibitory neurons in the pontine reticular formation (PRF) project to the intralaminar nuclei of the thalamus (IL). Selective activation of PRF-IL fibers evoked immediate behavioural arrest for the duration of stimulation. The strong motor response was surprising given that PRF has been implicated in arousal but not in motor control. In this study, we aimed to examine the inputs of the PRF inhibitory cells possibly carrying motor signals and the impact of these inputs on the activity of PRF inhibitory neurons. Retrograde tracer injected into the PRF labelled L5 pyramidal cells located selectively in the cingulate and M2 cortices as well as neurons in the deep cerebellar nuclei. This connectivity is consistent with a possible motor function but inconsistent with the presumed role in arousal. Injections of AAV-DIO-ChR2-mCherry into the M2/cingulate cortex of RBP4-Cre/Glyt2-eGFP double transgenic mice revealed that the entire PRF receives L5 inputs. Within PRF cortical afferents contacted mostly thin distal dendrites. Cortical inputs to GlyT2 cells were confirmed at the EM level. Juxtacellular recording and labelling in PRF under ketamine/xylazine anaesthesia demonstrated that rhythmic activity of Glyt2 cells was tightly linked to slow cortical oscillation and was disrupted upon spontaneous desynchronization. Pharmacological inactivation of the cortex led to decreased irregular firing of the GlyT2 neurons, whereas photoactivation of M2 L5 cells evoked short latency action potentials with high probability in PRF. These experiments together indicate strong motor cortical control over PRF-GlyT2 cells. In *in vitro* preparation optogenetic activation of M2 fibers reliably produced purely glutamatergic synaptic responses in PRF-GlyT2 cells. Both AMPA and NMDA receptors were functional at these synapses, which showed non-depressive behaviour during stimulation trains. Our results indicate that synchronous higher order motor (M2) cortical activity can reliably activate inhibitory neurons of the PRF, thus likely convey a behavioural signal computed by frontal, motor cortical regions. PRF GlyT2 cells in turn transfer this signal to the IL thalamus affecting thalamocortical and thalamostriatal activity.

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Poster

705. Cortical and Thalamic Circuits

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Program#/Poster#: 705.12/SS29

Topic: H.01. Animal Cognition and Behavior

Support: NINDS R01NS079518

Center for NeuroScience (CNS)

Title: Contributions of specific cell types to sensorimotor decision making

Authors: *J. ESSIG[1], G. FELSEN[2]
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Abstract: The midbrain superior colliculus (SC) is critical for selecting targets for movement, but the circuitry underlying this computation is not well understood. While contralateral targets are represented by the activity of SC neurons at specific locations in a well-described topographic map, little is known about the role of specific cell types in target selection. Approximately one-third of neurons in the SC are inhibitory and may function to shape inter- and intra-SC dynamics to direct behavior toward spatial targets. Here, we examine this idea by recording from optogenetically-identified inhibitory SC neurons in behaving mice. We first expressed channelrhodopsin-2 (ChR2) in GABAergic neurons via an AAV-mediated Cre-dependent construct delivered to the left SC of Gad2-Cre mice. Following virus injection, mice were trained on a two-alternative spatial choice task in which an odor delivered to a central port cued selection of the left or right reward port. Trained mice were then implanted with an "optetrode" drive, an optic fiber surrounded by four tetrodes, to enable light delivery to and extracellular recordings from the same population of SC neurons. Following each behavioral session, ChR2-expressing GABAergic neurons were identified based on short-latency light responses (i.e., "optotagging"); we then determined which neurons recorded during the task were GABAergic by comparing light-elicited waveforms to those collected during the behavioral session. We found GABAergic SC neurons exhibited increased activity during movement to the target (i.e., reward port), with mixed preferences for ipsilateral and contralateral movements. One potential function for this pattern of activity is to suppress nearby output neurons representing competing targets as the movement is executed, ensuring a unitary movement. Future studies will further delineate functional SC circuitry underlying target selection by examining the activity of projection-defined SC cell types (e.g., commissural cells or premotor output cells), and by determining the necessity and sufficiency of cell type-specific activity for target selection.

Disclosures: J. Essig: None. **G. Felsen:** None.

Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

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DFG, German Research Foundation Fellowship to S.R and A.V.S

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Title: A midbrain mechanism for computing instinctive escape behavior

Authors: *D. EVANS[1,2], S. RUEHLE[1,2], A. STEMPEL[1,2], R. VALE[1,2], T. BRANCO[1,2]
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Abstract: Animals face frequent threats from predators and must generate appropriate behavioral responses to ensure survival. To achieve this, they process sensory cues to estimate the presence and imminence of predatory threats, and transform this information into innate defensive actions. In this study, we have used a combination of behavioral and neurophysiological methods in the mouse to investigate how the decision to escape from predatory threats is computed.
First, we developed an innate decision making paradigm in which a mouse is presented with threats of varying intensity during foraging and chooses whether or not to escape to a shelter. The performance data in this assay show a gradual increase in escape probability and flight vigor with increasing threat intensity, a relationship that is well captured by a signal detection theory model of decision making where threat values are compared to an escape boundary. We then performed calcium imaging in freely-moving mice to probe for neural correlates of decision elements and flight behavior in brain areas necessary for the flight responses: we found that VGLUT2$^+$ neurons in the deep layers of medial superior colliculus (dSCm) gradually increase their activity during threat presentation, while activation of VGLUT2$^+$ neurons of the dorsal periaqueductal gray (dPAG) coincides with escape initiation. Optogenetic activation of dSCm-VGLUT2$^+$ neurons in vivo recapitulates the statistics of escape probability evoked with threatening stimuli, while activation of VGLUT2$^+$ neurons in the dPAG evokes escape responses in an all-or-nothing manner. Finally, using monosynaptic G-deleted rabies tracing and channelrhodopsin-2-assisted circuit mapping, we show that over half of dPAG-VGLUT2$^+$ neurons receive monosynaptic connections from dSCm-VGLUT2$^+$ neurons via low release probability synaptic connections that act as a high-pass activity filter.
These results suggest excitatory neurons in the dSCm encode evidence of threat, which is thresholded by dPAG neurons to determine whether or not escape is initiated. Our findings provide a mechanism for the computation of escape decisions, and advance our understanding of how neurons process information in a circuit critical for implementing basic behaviors.

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Poster

705. Cortical and Thalamic Circuits

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Program#/Poster#: 705.14/SS31

Topic: H.01. Animal Cognition and Behavior

Support: Hope for Depression Research Foundation

NIH K08 MH109735

Title: An accessible method for chronic social defeat stress in female mice

Authors: *A. HARRIS[1,2], Z. H. BRETTON[1], P. ATSAK[2], E. S. HOLT[1,4], R. ALAM[1,4], M. P. MORTON[1], A. I. ABBAS[1,3], E. D. LEONARDO[1], S. S. BOLKAN[1], R. HEN[1,3], J. A. GORDON[5]
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Abstract: Historically, female subjects have been omitted from preclinical stress studies, despite evidence that women are more liable to develop anxiety and depression. In particular, studies of stress susceptibility and resilience have focused on males since the commonly used paradigm -- chronic social defeat stress -- does not work in females. By using pheromones to increase resident male aggressive behavior, we have developed a readily accessible version of this paradigm that can be used in female mice. Using this approach, we find that female mice that undergo repeated social defeat stress develop social avoidance (Wilcoxan rank sum; $p<0.001$), decreased sucrose preference ($p<0.05$) and spend less time in the open arms of the elevated plus maze ($p<0.05$) relative to control mice. Moreover, a subset of the female mice who undergo repeated aggression display resilience, maintaining control levels of social exploration and sucrose preference. This method closely follows a standard protocol used for chronic social defeat stress in male mice and produces similar results to those obtained in male mice. We anticipate that the development of this easy-to-use method for social defeat stress in female mice will greatly facilitate the inclusion of female subjects in stress research.

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Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 705.15/SS32

Topic: H.01. Animal Cognition and Behavior

Support: NARSAD Young Investigator Grant 24848

Title: The role of prefrontal interneuron subtypes in working memory

Authors: *A. I. ABBAS[1], M. J. M. SUNDIANG[1], E. MYHRE[1], B. HENOCH[1], M. P. MORTON[1], S. S. BOLKAN[1], A. Z. HARRIS[1], C. KELLENDONK[1], J. A. GORDON[2]
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Abstract: Schizophrenia has previously been hypothesized to result from a failure of functional connectivity in the brain. Accumulating evidence supports this view, though the cellular mediators of functional connectivity within the brain are not well understood. Given data showing that two classes of inhibitory neurons, parvalbumin- (PV) and somatostatin-expressing (SOM) interneurons, exhibit abnormal expression of markers, GABA synthetic enzyme, and GABA transporter in individuals with schizophrenia, we hypothesized that prefrontal cortical interneurons support working memory by facilitating functional connectivity. To test this hypothesis, we used the light-activated proton pump Arch3.0 to selectively silence prefrontal PV or SOM interneurons in the medial prefrontal cortex of mice performing the delayed non-match to sample T-maze test of spatial working memory. We simultaneously recorded neural activity in the medial prefrontal cortex (mPFC) and other brain areas known to be involved in working memory, including the dorsal and ventral hippocampus (dHPC and vHPC), and mediodorsal thalamus (MD). We used measures of LFP-LFP and spike-LFP synchrony to characterize the functional connectivity between these various structures. Silencing SOM interneurons during the sample or delay phases of the task significantly impaired working memory performance when the delay length was 10 seconds or 60 seconds. SOM silencing during the sample phase of the working memory task was also associated with a decrease in phase locking, as measured by PPC, between mPFC neurons and vHPC theta oscillations and dHPC theta oscillations. SOM silencing during the sample phase was also associated with impaired spatial representations of goal location by mPFC neurons. Silencing PV interneurons had no effect on working memory behavior, functional connectivity, or spatial representations in the mPFC. Our evidence is consistent with SOM interneurons supporting spatial encoding during working memory and facilitating hippocampal-prefrontal synchrony. These findings suggest that interneuron dysfunction may contribute to cognitive deficits in schizophrenia by disrupting long range synchrony between the hippocampus and prefrontal cortex.

Disclosures: **A.I. Abbas:** None. **M.J.M. Sundiang:** None. **E. Myhre:** None. **B. Henoch:** None. **M.P. Morton:** None. **S.S. Bolkan:** None. **A.Z. Harris:** None. **C. Kellendonk:** None. **J.A. Gordon:** None.

Poster

705. Cortical and Thalamic Circuits

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 705.16/SS33

Topic: H.01. Animal Cognition and Behavior

Support: Hope for Depression Research Foundation

Title: Frequency-specific facilitation of hippocampal-prefrontal transmission increases anxiety-like behavior

Authors: *N. PADILLA COREANO[1], S. E. CANETTA[2], E. TEBOUL[3], A. GARCIA-GARCIA[3], R. WARREN[3], C. KELLENDONK[3], J. A. GORDON[4]
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Abstract: Avoidance of potentially dangerous locations, such as the open arms of an elevated plus maze, has been used to study the neural circuitry underlying conflict-based anxiety-like behavior in rodents and may be of relevance to human anxiety disorders. We and others have demonstrated a key role for the ventral hippocampus (vHPC) and the medial prefrontal cortex (mPFC) in these behaviors (Kjelstrup et al., 2002; Maren and Holt, 2004; Shah and Treit, 2003). Exposure to anxiogenic environments enhances synchrony between the vHPC and mPFC, specifically in the theta-frequency (4-12 Hz) range (Adhikari et al., 2010), facilitating the construction of neural representations of aversion within the mPFC (Adhikari et al., 2011; Padilla-Coreano et al., 2016). Optogenetic inhibition of the direct projections from the vHPC to the mPFC ablates these representations and reduces both theta-frequency synchrony and avoidance behavior (Padilla-Coreano et al, 2016; Kjaerby et al., 2016). The specific relevance of theta-frequency activity, however, remains unclear. Here we dynamically modulated vHPC terminals in the mPFC using optogenetic stimulation. Terminal activation with an 8 Hz, but not 20 Hz, oscillatory stimulus was sufficient to increase avoidance behavior, while surprisingly pulsatile 8 Hz stimulation had no effect on behavior. *Ex vivo* and *in vivo* neural recordings demonstrated that the 8 Hz oscillatory stimulus entrained neural activity in the entire vHPC-mPFC network, particularly during exposure to an anxiogenic environment. These data support the importance of theta-frequency activity in vHPC-mPFC communication for the regulation of anxiety-like avoidance behavior.

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Poster

705. Cortical and Thalamic Circuits

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Program#/Poster#: 705.17/SS34

Topic: H.01. Animal Cognition and Behavior

Support: Irma Hirschl Trust

R01 MH096274

F31 MH102041

F30 MH107204

Hope for Depression Research Foundation

Title: Thalamic projections sustain prefrontal activity during working memory maintenance

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Abstract: The mediodorsal thalamus (MD) shares reciprocal connectivity with the prefrontal cortex (PFC) and decreased MD-PFC connectivity is observed in schizophrenia patients. Patients also display cognitive deficits including impairments in working memory, but a mechanistic link between thalamo-prefrontal circuit function and working memory is missing. Here, using pathway-specific inhibition we found directional interactions between MD and medial PFC (mPFC), with MD-to-mPFC supporting working memory maintenance and mPFC-to-MD supporting subsequent choice. We further identify mPFC neurons that display elevated spiking during the delay, a feature that was absent on error trials and required MD inputs for sustained maintenance. Strikingly, delay-tuned neurons had minimal overlap with spatially-tuned neurons and each mPFC population exhibited mutually exclusive dependence on MD and hippocampal inputs. These findings indicate a role for the MD in sustaining prefrontal activity during working

memory maintenance. Consistent with this idea we found that enhancing MD excitability was sufficient to enhance task performance.

Disclosures: S.S. Bolkan: None. **J.M. Stujenske:** None. **S. Parnaudeau:** None. **T.J. Spellman:** None. **C. Rauffenbart:** None. **A.I. Abbas:** None. **A. Harris:** None. **J.A. Gordon:** None. **C. Kellendonk:** None.

Poster

706. Executive Function in Learning and Memory

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 706.01/SS35

Topic: H.01. Animal Cognition and Behavior

Support: Touro University Grant Award

Title: Environmental enrichment impacts place avoidance memory in zebrafish

Authors: *J. NISSANOV[1], T. VICKERY[2]
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Abstract: Environmental enrichment has been shown to enhance learning and memory retention in vertebrates. We assessed if this holds true for zebrafish tested on place avoidance, a one-trial learning paradigm. To do so, juveniles were reared in either a control environment consisting of bare tanks or in tanks containing a complex maze of objects. They were trained and then each tested once at a later time point and the degree of memory decrement assessed. The training and test apparatus consisted of a shuttle box divided into a lit and a dark compartment. To train and test, fish where placed in the disfavored compartment and a shock was delivered once they entered their prefered half of the box. The fish were removed and, for testing, transferred back into the disfavored compartment of the shuttle box. The latency time to swim to the preferred compartment, as measured off video, dropped to baseline more slowly for the experimental over the control group. The differential performance observed establishes that environmental enrichment does alter memory decrement in a one-trial place avoidance paradigm. This simple memory assessment is amendable to large-scale pharmacological, toxicological, and genetic studies on the interaction between organism and its environment.

Disclosures: J. Nissanov: None. **T. Vickery:** None.

Poster

706. Executive Function in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 706.02/SS36

Topic: H.01. Animal Cognition and Behavior

Title: Cognitive deficit correlated with changes in neuronal activity in Disc1$^{\Delta 2\text{-}3/\Delta 2\text{-}3}$ mice in touchscreen-based visual discrimination task

Authors: *B. WULAER[1], T. NAGAI[1], A. SOBUE[1], K. KURODA[2], K. KAIBUCHI[2], T. NABESHIMA[3], K. YAMADA[1]
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Abstract: Cognitive deficit is one of core symptoms in schizophrenia. Genetic and functional studies have implicated Disrupted-in-Schizophrenia 1 (DISC1), a risk gene for multiple mental disorders, in cognitive function. Altered expression of DISC1 has been identified in schizophrenia. To explore its function, we have previously generated mice lacking exons 2 and 3 of the Disc1 on a C57BL/6J genetic background (Disc1$^{\Delta 2\text{-}3/\Delta 2\text{-}3}$ mice). In the present study, to evaluate the dorsal striatum-dependent associative learning and behavioral flexibility in Disc1$^{\Delta 2\text{-}3/\Delta 2\text{-}3}$ mice, we observed performance of the mice in a translatable touchscreen-based visual discrimination task. To study whether the abnormal behavior observed in the visual discrimination task was accompanied by differences in neuronal activity, we used c-Fos immunohistochemistry to examine the patterns of activation on the first and last visual discrimination learning session. The total number of c-Fos immuno-positive cells was counted in the dorsal striatum. Finally, the effect of clozapine in Disc1$^{\Delta 2\text{-}3/\Delta 2\text{-}3}$ mice in visual discrimination task was also analyzed. Disc1$^{\Delta 2\text{-}3/\Delta 2\text{-}3}$ mice exhibited retarded performance in the visual discrimination task, which was mainly due to high perseverative response compared to wild-type animals. c-Fos expression was specifically increased in the dorsomedial, but not dorsolateral striatum after the first visual discrimination day in Disc1$^{\Delta 2\text{-}3/\Delta 2\text{-}3}$ mice compared to the wild-type animals. The daily treatment of clozapine ameliorated the impairment by normalizing the preservative behavior. These results show that enhanced repetitive and compulsive-like behaviors in Disc1$^{\Delta 2\text{-}3/\Delta 2\text{-}3}$ mice may lead to cognitive impairment. Daily treatment with clozapine could ameliorate the impaired performance. Hyperactivity in Disc1$^{\Delta 2\text{-}3/\Delta 2\text{-}3}$ mice in the dorsomedial striatum might be responsible for the abnormal phenotype.

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Poster

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Support: NRF-2015M3 C7A1031969

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SRC-2014051826

BK21+ program

Title: Functional significance of the repetition suppression of the neural firing in the perirhinal cortex during object recognition

Authors: J. AHN, Y. KIM, *I. LEE, PhD
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Abstract: It has been suggested that cells in the medial temporal lobe (MTL) signal relative familiarity of a stimulus by subsequently decrementing their response magnitude toward a repeated stimulus. The phenomenon called “repetition suppression” has been implicated as a potential neural substrate for recognition memory. It remains unknown, however, whether the repetition-sensitive neurons in the MTL can correlate with actual recognition behavior. To investigate this issue, we trained rats (n=7) in an object-cued response selection task. Experiments were performed on a linear track (46 x 7.5 cm) with a custom-made response box (13 x 6 x 13 mm) positioned at the other end of the track. One of two perceptually distinct 3-dimensional object stimuli (House and Icecream) was attached to the box, and the rat had to produce a differential response (e.g., pushing or nose-poking) to the box depending on the identity of the object. Rats were trained to criteria (>= 75% correct performance for 2 consecutive sessions) with the two objects, and underwent surgery to implant a microdrive targeting the hippocampus (HIPP) and perirhinal cortex (PER) simultaneously. During recording sessions, a pair of novel objects (Phone and Owl) were introduced and presented along with the familiar objects in an intermixed fashion. Cells in both regions (n=121 in HIPP and n=59 in PER) responded to the objects by significantly decrementing or incrementing their firing rates as the same objects were repeated within a session. Most of the PER neurons (37/59) showed a selective response toward a particular object stimulus, whereas a smaller proportion of neurons (39/121) did so in the HIPP. PER neurons were more likely to alter their response toward novel objects (n=23) than familiar ones (n=14). In the HIPP, the number of neurons responding to novel (n=19) and familiar objects (n=20) was similar. We also measured the slope of the

response change by fitting a linear regression model to the trial-by-trial firing rates for each object. In both regions, the magnitude of the slope tended to be higher for less familiar objects. It is expected that our preliminary results shed light on the novel functional aspect of the repetition-sensitive neurons in the MTL.

Disclosures: J. Ahn: None. **Y. Kim:** None. **I. Lee:** None.

Poster

706. Executive Function in Learning and Memory

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Program#/Poster#: 706.04/SS38

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant HD080679

Title: Role of feedback and statistical density in rat visual category learning

Authors: *M. B. BROSCHARD[1], J. KIM[1], L. CASTRO[1], E. A. WASSERMAN[1], V. M. SLOUTSKY[2], J. H. FREEMAN[1]
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Abstract: Categorization is a fundamental process underlying adaptive behavior. Human visual category learning is influenced by the statistical density of category-relevant features and the level of supervision (Kloos & Sloutsky, 2008, JEP: General, 137, 52-72). The current experiment examined the roles of statistical density and supervision in visual category learning in rats. Using an operant chamber outfitted with a touch screen, four groups of rats (n = 6 per group) were either presented with 'high density' stimuli (three of five features were category-relevant) or 'low density' stimuli (one of five features was category-relevant) and either under 'high supervision' (food reward was given only for correct responses) or 'low supervision' (food reward was given for all responses). Accuracy for each category was recorded and criterion was defined as 75% correct on both categories for two consecutive sessions. After meeting the training criterion, the rats were given testing sessions in which training stimuli were mixed with probe trials. Probe trials included novel exemplars (novel irrelevant features), relocated stimuli (in which the relevant features appeared in different locations), and singleton stimuli (only one relevant feature was presented). All rats in the high density-high supervision condition (6/6) showed rapid learning of the two categories. They also showed very high accuracy with novel stimuli. Accuracy dropped significantly when rotated or singleton stimuli were presented, suggesting that the rats' representations of the categories included feature-location binding. Some of the rats in the low density-high supervision condition (2/6) learned and showed substantial generalization to novel exemplars. Like rats in the high density-high supervision

condition, rats in the low density-high supervision condition that learned showed a significant drop in accuracy during presentations of the rotated and singleton test stimuli. Rats trained in the high density-low supervision and low density-low supervision conditions did not learn. Only one rat in the high density-low supervision condition reached criterion performance. The results indicate that unlike humans, rats require supervision to learn both high and low density categories. Moreover, humans consistently learned in the low density-high supervision condition. The species differences in category learning may be related to differences in medial prefrontal and/or hippocampal function.

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Poster

706. Executive Function in Learning and Memory

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Program#/Poster#: 706.05/SS39

Topic: H.01. Animal Cognition and Behavior

Support: NINDS 1R25NS094094

Title: Lateral habenula inactivation impairs delayed alternation performance but not working memory in rats

Authors: *P. M. BAKER, E. M. GARCIA, B. K. LEUNG, S. J. Y. MIZUMORI
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Abstract: The lateral habenula (LHb) has been implicated in behaviors that are reliant on working memory to perform. However, it is unclear whether these deficits are due purely to an inability to recall aspects of the task required to solve it or an inability to apply the rule requiring working memory. In order to address this, we employed a delayed spatial alternation task in which naïve rats perform significantly above chance levels due to an innate preference for choosing arms less recently visited. Specifically, a modified automated plus-maze was used in which two arms (east and west) were designated as reward arms and two arms (north and south) were designated as start arms. Prior to behavioral testing, male Long-Evans rats were implanted with bilateral cannula aimed at the LHb. After recovery, rats were pretrained to explore maze arms by obtaining rewards in reward arms and then returning to start arms. Once rats performed this sequence at least 45 times over 30 min, they began test sessions. On a given test trial, a rat was placed on a start arm (pseudorandomly chosen). After a 10 sec delay, the two reward arms were presented simultaneously. The rat was required to choose the arm that was least recently visited in order to receive two 45mg sugar pellets. A repeat choice was not rewarded. Rats were randomly divided into three groups: saline - saline treatment (Sal-Sal); saline - inactivation (Sal-

Inact); and inactivation - saline (Inact-Sal). LHb Inactivation was accomplished by administration of the GABA agonists, baclofen and muscimol (50ng/0.2µL) 6 min prior to testing. Treatments occurred either during the first three days of the test sessions (Learning), or for three days after at least 80% correct alternations (Asymptote). If an animal was unable to recall the arm it had last visited, then chance performance would be predicted. However, inactivation during the learning state resulted in above chance performance ($t_{(2)} = 7.94$, $p = 0.015$) with no differences between treatment groups ($F_{(2,32)} = 0.37$, $p = 0.70$). In contrast, inactivation during asymptotic performance led to a significant impairment in performance ($F_{(2,32)} = 30.09$, $p < 0.01$). Overall, these results indicate that the LHb is not involved in working memory per se, but rather in conditions in which a learned strategy must be enacted utilizing working memory.

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Poster

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Instituto Presbiteriano Mackenzie

Title: Single episode of neonatal status epilepticus impairs sociability but not cognitive function in rats

Authors: *R. M. CYSNEIROS[1], A. PACÍFICO[2], S. P. BATISTA[2], P. BASTOS[2], G. L. BARBOSA[2]
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Abstract: A single episode of *status epilepticus* (SE) in rats produce an autistic phenotype, characterized by social play impairment, low preference by novelty and deficit in social discrimination unrelated with emotionality, but the underlying mechanism is unknown. We investigated memory of social recognition and cognitive function in adults male rats subjected to a single episode of neonatal SE induced by pilocarpine (380 mg/kg, ip) at PN9. Social memory was assessed using habituation/deshabituation paradigm and cognitive function was assessed

using T maze and Operant conditioning paradigms. Gene expression for oxytocin (OT) and oxytocin receptor (OTR) was assessed in hippocampus (HP), amygdala (AMG) and hypothalamus (HYP). In habituation/deshabituation paradigm experimental animals spent less time investigating the unfamiliar conspecific (F(1,124)=5.64, p= 0.023) and no difference in investigation was noted when the conspecific was replaced by a new social stimulus. In operant conditioning, the number of sessions for associative learning did not differ between groups (t=0.45, gl=12, p=0.65). The continuous reinforcement (CRF) did not differ between groups ($F_{[1,36]}$= 0.018, p= 0.89) but increased across sessions ($F_{[3,36]}$= 9.51, p< 0.0001), suggesting acquisition of associative learning and formation of long-term memory. In the discriminative stimuli, the percentage of corrects response did not differ between groups ($F_{[1,108]}$ = 2.12, p= 0.17) but increased across sessions ($F_{[9,108]}$ = 9.14, p < 0.0001), suggesting no changes in working memory. In forced-alternation task, the accuracy increased across sessions ($F_{[3,69]}$=4.32, p=0.007), with no difference between groups ($F_{[1,69]}$=0.45, p= 0.50). In the left-right discrimination task, the percentage of corrects responses did not differ between groups ($F_{[1,69]}$=1.58, p= 0.22) and increased across session ($F_{[9,69]}$=10.33, p<0.0001), suggesting no difference in reference memory. In behavioral flexibility task, the percentage of corrects responses did not differ between groups ($F_{[1,69]}$=3.87, p= 0.061) but increased across session ($F_{[9,69]}$=37.21, p<0.0001). In the gene expression, mRNA for OT did not differ between groups in HP, (t(8)= 0.53, p= 0.61), HYP (t(8)= 0.82, p=0.10) and AMG (t(8)= 0.81, p= 0.43). For the OTR, mRNA expression was significantly lower in the HP (t(8)= 2.43, p = 0.04), but not differences was noted in AMG (t(8)= 0.85, p= 0.45) or HYP(t(8)= 0.58, p= 0.58). We showed that a single neonatal SE does not impair cognitive function but produce impairment of social recognition memory may be related to decrease of OT signaling in hippocampus.

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Poster

706. Executive Function in Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: SUNY-OW Faculty Development Grant

Title: Developmental lead exposure reduces encephalization and cortical quotients resulting in dysexecutive functions in the rat

Authors: *L. S. NEUWIRTH[1], Y. KIM[2], S. R. RUBI[3], S. KAUR[4], N. MATHEW[4], S. MASOOD[4], B. TRANQUILLE[3], V. THIRUVERKADU[3], T. J. JOSE[4], C. JO[3], T. F. DACIUS, Jr.[4], J. R. BONITTO[3], J. C. SKEEN[3], A. ALVIRA[4], E. KHAIRI[3], A. IQBAL[4]

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Abstract: Lead (Pb) is a developmental neurotoxin that causes lifelong cognitive executive dysfunction. However, it is unclear how developmental exposure to Pb effects cortical volume and a variety of neurochemical signals which are responsible for not only regulating cognition, but also global brain excitability. Here we evaluated how Pb exposure alters cortical volume and neurochemical signaling in the adult rat brain following developmental exposure to Pb. We hypothesized that developmental Pb exposure would decrease cortical volume and increase brain excitability by reducing GABA levels and the ratio of GABA to other important neurotransmitters (i.e., glutamate, dopamine, norepinephrine, epinephrine, serotonin, and taurine) as a function of Pb exposure and sex. Results show that dependent upon the developmental time-period of Pb exposure and sex, that Pb differentially reduces cortical volume. The neurochemical analysis revealed differences in the patters of neurotransmitter profiles in specific brain regions (i.e., PrL = prelimbic cortex, IL = infralimbic cortex, OV = ventral orbital frontal cortex, OVL = ventrolateral orbital frontal cortex, dHP = dorsal hippocampus, & vHP = ventral hippocampus) dependent upon sex and developmental time-period of exposure. Our data suggest an emerging profile of which neurotransmitters in specific regions of the rat brain may contribute to cognitive dysexecutive functions and accompanying learning and memory problems associated with the attention set-shift task (ASST).

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Poster

706. Executive Function in Learning and Memory

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NIH Grant AG019610

Title: Advanced techniques for characerizing rodent brains with diffusion MRI

Authors: ***L. DO**[1], A. BERNSTEIN[1], P. K. BHARADWAJ[2], G. E. ALEXANDER[2], C. A. BARNES[3], T. TROUARD[1]

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Abstract: Diffusion magnetic resonance imaging (DMRI) can help to characterize neurological processes, such as cognitive aging. Rodent models are important tools for seminal investigations of such processes, however methods designed for analysis of human DMRI data have not been well translated to rodents. The purpose of this study is to evaluate a preprocessing pipeline that has been optimized for rodent brain imaging. Fisher 344 rats (n=7) underwent 3D T2-weighted RARE (150 micron isotropic) and 64 direction diffusion weighted single shot echo planar imaging sequence at b=1000, 2000, and 3000 s/mm^2, on a 7T Bruker Biospec MRI scanner. DMRI data were semi-automatically brain extracted using *ITKsnap* and *MRIcron*, bias field corrected using *N4ITK* implemented in *ANT*s, EPI distortion corrected using *TOPUP* within *FSL*, eddy current distortion correction using *EDDY* within *FSL* and de-noised using local principal component analysis in *MATLAB*. Diffusion tensors were estimated using a weighted linear least squares fit of the diffusion data and derived scalar maps including fractional anisotropy and mean diffusivity were computed with *MRTrix*. Manual brain extraction of the 3D RARE images took 4±1 hours whereas the semi-automated method took 4±0.5 minutes. The dice coefficients (DC) indicating overlap between manual and semi-automated methods with a N4 bias field correction were higher than those obtained when the bias field correction was **not** applied. Applying non-parametric Wilcoxon Signed Rank Test revealed significance between the DCs (Z-score = -2.366, p = 0.018. Eddy current correction effectively eliminated distortions between DMRI scans, but *TOPUP* failed to completely remove the EPI distortion as evidence by the remaining signal pile up at the bottom of the brain. Results show automated brain extraction produces similar accuracy compared with the manual method while reducing analysis time in 3D RARE images. Furthermore, distortion correction, eddy current corrections, and noise reduction followed by bias correction show improvement in image quality in the minimization of distortions in DMRI images. Further testing is needed with a larger cohort and refinement of the pipeline to further minimize the pile up artifact not addressed by *TOPUP* by registering the images to a T2 anatomical space. The bias field correction step in automated brain extraction maintained the accuracy of the manual method while also reducing analysis time in T2-weighted 3D RARE data. Preprocessing of DMRI data show that this pipeline has the potential to be implemented in rat brain data to minimize distortions resulting from the collection scheme.

Disclosures: L. Do: None. **A. Bernstein:** None. **P.K. Bharadwaj:** None. **G.E. Alexander:** None. **C.A. Barnes:** None. **T. Trouard:** None.

Poster

706. Executive Function in Learning and Memory

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Title: Decoding brain areas using the local field potential

Authors: *S. J. HOFFMAN, N. M. DOTSON, C. M. GRAY
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Abstract: Neuronal oscillations are widely believed to play a key role in the coordination of neural activity. However, little is known about the regional and temporal variations in the local field potential (LFP) during cognitive tasks. To elucidate the large-scale spatio-spectral patterns of activity underlying visual working memory, we developed a large-scale semi-chronic recording system that enables the long-term measurement of neuronal activity from up to 256 independently movable microelectrodes spanning an entire cerebral hemisphere in non-human primates. We implanted this instrument in two macaque monkeys and recorded neuronal activity for 6 and 9 months, respectively, while the animals performed an object-based, delayed match-to-sample (dMTS) task and a set of control tasks. In total, we obtained recordings of neuronal activity from over 60 separate cortical areas and subcortical structures. To determine if each cortical area has a distinct spectral signature, we trained a machine learning classifier to decode cortical areas using LFPs. We find that cortical areas can be reliably predicted based solely on properties of the LFP. These findings show that there are robust anatomically correlated variations in the LFP power spectra. Additionally we found task dependent variations during the delayed match-to-sample task. These variations were heterogeneous and dispersed broadly, indicating task dependent changes in LFP power occur across the brain.

Disclosures: S.J. Hoffman: None. **N.M. Dotson:** None. **C.M. Gray:** None.

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Title: Iterated Prisoner Dilemma boost the emergence of high reciprocal altruism-based cooperative behaviors in rats

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Abstract: The underlying mechanisms that explain cooperative behaviors among unrelated remain unclear in evolution theory. However, it was shown that the use of appropriate 2x2 pay-off matrices in the iterated Prisoner Dilemma (iPD), boost the emergence of reciprocal altruism-based cooperative behaviors, as a way to learn to maximize reward. When subjects face an opponent with cooperative strategy (Tit for Tat) and iPD matrix, the biggest long-term reward is available when both actor and opponent subjects cooperate mutually. It happens when mutual cooperation is the most probable state out of the four possible states in the game. Although, iPD is successfully learnt in humans it has not been found in animals. Here, we show for the first time that using a specific pay-off matrices and punishment (timeout), *long-Evans* rats were able to learn reciprocal altruism behaviors with cooperation rates over 80%. Two groups of unrelated male Long-Evans rats (two months old) were trained using dual opposite operant chambers, visual contact between animals was allowed through a small window. The experimental and opponent groups were food restricted in order to maintain their weights at 90-95% and 80%-85% of their *ad libitum* weights, respectively. When modeled as *Markov chain transition probabilities,* rats behaviors show a strong preference to stay in the mutual cooperation state or to return to it as soon as a wrong response is executed.

Disclosures: G. Delmas: None. **S.E. Lew:** None. **B.S. Zanutto:** None.

Poster

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Topic: H.01. Animal Cognition and Behavior

Support: DFG Research Unit 1581

Title: What you see is what you get? - Testing predictions of overexpectation derived from the Rescorla-Wagner model

Authors: *J. PACKHEISER[1], R. PUSCH[1], O. GUNTURKUN[1], M. UENGOER[2]
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Abstract: Learning about the predictive power of stimuli for appetitive or aversive events is a crucial ability for an organism's survival. The Rescorla-Wagner model has been used in various research fields to predict the behavior during learning processes. It bases its predictions on changes in associative strength of stimuli in relation to the discrepancy between the predicted and actual outcome. The model has been validated for many behavioral paradigms to accurately model natural learning in humans and non-human animals. One of the many predictions offered by their model concerns the role of overexpectation. Overexpectation refers to extinction that occurs after learning positive (excitatory) associations with two individual stimuli A+ and B+. If these stimuli are then presented together as the compound AB+, extinction will occur if the amount of reward is not increasing accordingly meaning that the amount of reward is doubling. We conducted an experiment using pigeons (*Columba livia*) to evaluate a novel prediction related to the effects of overexpectation. The model predicts a total loss in associative strength for A+ during the presentation of the compound if B+ is still presented individually and is continuously rewarded. Additionally, we tested whether a novel stimulus Z paired with an initially learned stimulus C+ followed by no reinforcement (CZ-) functions as a conditioned inhibitor. Here, overexpectation by the Rescorla-Wagner model predicts no total loss of the associative strength of C as Z gains negative associative value. Our results revealed that neither the prediction for A+ nor C+ holds true. A+ did not decrease in associative value during the process of overexpectation, whereas C+ demonstrated an absolute loss of associative strength. We conclude that the Rescorla-Wagner model is not sufficient to systematically anticipate learning in every conceivable condition. Instead, it appears to be more accurately estimated by configural theories of learning.

Disclosures: J. Packheiser: None. **R. Pusch:** None. **O. Gunturkun:** None. **M. Uengoer:** None.

Poster

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Support: Grants-in-Aid for Scientific Research on Innovative Areas (26250003; 25119004)

Title: Hasty decision-making delays accomplishment of learning

Authors: *Y. YAWATA, K. MAKINO, Y. IKEGAYA
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Abstract: For appropriate decision-makings, rapidness and correctness of decisions are both important. However, little is known about the relationship between the length of time required to decision-making and the overall task performance. In this study, we conducted a nose-poke behavior test in which rats were rewarded by poking their noses into one of two holes in an operant chamber. Either one of the two holes was randomly illuminated as a light cue, which indicated the incorrect hole (no reward delivered). All rats reached the learning criterion of 80% correct rate within a 4-d task, in which the number of sessions to the criterion varied across animals. The number of omission (i.e., trials without nose poking) increased transiently immediately before the learning performance reached the criterion. We found that rats with shorter latencies to poke spent more sessions to reach the learning criterion (i.e., slow learners). Although the latencies in correct trials (LC) was significantly longer than those in incorrect trials (LI), rats with low LI / LC ratios learned more slowly. These results suggest that earlier decision-making do not provide benefits to task performance and that deliberative decision-making is more crucial for learning than correctness in each trial.

Disclosures: Y. Yawata: None. **K. Makino:** None. **Y. Ikegaya:** None.

Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH081153

Title: Gaussian process regression for inferring the temporal evolution of neuronal activity during within-session learning in monkeys

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Abstract: Uncovering the relationship between behavioral performance and neuronal activity during learning is one of the hardest problems in Neuroscience. Classical analysis tools work best for data acquired during steady-state behavior, which means the subject must be overtrained on a particular task to satisfy the assumptions of the statistical model. Overtraining avoids problems arising from non-stationary data, but precludes any attempt to study learning itself. Statistical methods used for machine learning applications may be useful for analyzing data

where the underlying rates vary within and across trials. We present here an application of Gaussian process regression (GPR), a non-parametric method based on Gaussian process priors for inferring probabilistically varying firing rate functions. We used this method to model real-time changes in firing rate in recordings from neurons in parietal area LIP in monkeys during a transitive inference task. In each session, which lasted 20-30 minutes, subjects were presented with never-before-seen photographic stimuli, and learned how those stimuli were implicitly ordered through trial and error responding. Performance was necessarily at chance levels (50% correct) at the start of each session, but gradually improved to 70% (on average) over the course of ~630 trials. As a multivariate regression procedure, Gaussian processes relates the neural response to all explanatory variables of interest at once. In this approach, the spike trains are considered as a Cox process (i.e. a mixture of Poisson processes) whose rate parameters are governed by a posterior distribution of *Gaussian processes.* These rates are thus recovered from the covariance structure of the data itself. *This allows the changing firing rates to be estimated without presupposing the functional form of the time series*. Underlying rate fluctuations derived from GPR can be compared to behavioral performance changes, which may also be modeled as a Gaussian process. In conclusion, we can explore the evolution of the neural response as a function of explanatory variables (e.g. stimulus rank) and reveal the emerging tuning in direct relation to learning.

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Poster

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1 R01 EY017039-07

1P30 EY019007-06

Title: Cerebellar simple spikes report the trial outcome during sensorimotor learning

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Abstract: The cerebellum (CB) plays a key role in motor learning, and there is a consensus that its role is to identify motor errors and correct the movement. However, recent tract-tracing and

fMRI connection studies have shown that the CB is reciprocally connected to areas such as prefrontal cortex that are far removed from the details of motor control. In keeping with these anatomical data, we have shown that Purkinje cells in monkey mid-lateral cerebellum track the learning of arbitrary visuomotor associations in a manner in which there were no obvious changes in the kinematics of the movement (Ipata et al. SfN 2014,2015; Sendhilnathan et al. NCM 2017). We trained two monkeys on a visuomotor association task, which began when the monkeys grasped two bars, one with each hand, after which a fixation point appeared for 800 ms. Then one of a pair of symbols appeared at the center of gaze. One symbol signaled the monkey to release the left bar and the other to release the right bar. The monkey was rewarded for releasing the hand associated with that symbol. We began by presenting the monkey with the same over-trained symbol pair every session, and after a number of trials, changed the symbol pair to two novel symbols that the monkey had never seen before. Over 20 to 40 trials, the monkey gradually learned which symbol was associated with which hand. When the monkey had learned the new association, we reversed the pairing. The monkey usually took longer (40 to 60 trials) to learn the reversal. When we brought back the over-trained symbol pair, the monkey performed perfectly without making any error. Although the reaction time of the response increased at the symbol change the monkey made the same movements in response to well-learned and newly changed symbols. The majority of cells responded equivalently when the monkey moved either hand. The simple spike activity of Purkinje cells has a memory of the trial's outcome, during the visuomotor association learning period. Neurons that report the prior trial's outcome show change in firing activity in the fixation, symbol, and pre-movement epochs, while neurons that report the current trial's outcome show change in firing rate after the reward period. We also identified a small group of neurons that report the prior trial's outcome as well as the current trial's outcome. This firing rate change occurred in a specific short epoch of the trial for a given neuron, and across the sample the change in activity of the cell sample continuously tiled the entire trial duration. This epoch-specific trial-to-trial difference decreased, for both groups, as the monkey learned the association, so that, after the learning phase, the difference in activity did not change.

Disclosures: N. Sendhilnathan: None. **M. Semework:** None. **M.E. Goldberg:** None. **A.E. Ipata:** None.

Poster

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Title: Input pathways for value-coded visual responses in midbrain dopamine neurons

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Abstract: Responses of midbrain dopamine (DA) neurons can reflect reward prediction errors that are thought necessary to acquire classically conditioned responses triggered by predicting sensory stimulus (Schultz., 1998). This learning is important to anticipate and acquire reward, or to avoid punishments. However, the neural mechanisms by which sensory inputs are conveyed to the ventral midbrain and the computational processes required to transform them into the reward prediction error signals remain to be determined.In the case of visual associative learning, the visual information is most likely conveyed to DA neurons either via the primary visual cortex (V1), and/or the midbrain superior colliculus (SC). In our previous study with macaque monkeys, we reported that the visual signals mediated via the SC are required elicit conditioned responses and to generate value-coded responses in DA neurons when V1 was disabled. However, while SC are exquisitely sensitive to retinal luminance change, SC neurons are largely insensitive to color, high spatial frequencies (form), and texture. Thus, in cases where conditioned stimuli are discriminated according to these additional features, it is likely that visual processing in V1 would be required.To address this question, we investigated whether visual signals originating in V1 can activate midbrain DA neurons in monkeys with unilateral lesions of V1. This was achieved by inactivating the SC with a unilateral microinjection of $GABA_A$ receptor agonist, muscimol, on the side of the brain where cortical visual processing remained intact. In our experimental paradigm, we simultaneously observed the animals' ability to exhibit classically conditioned anticipatory licking prior to the delivery of juice-reward, and responses of DA neurons evoked by conditioned visual stimuli presented to the visual field where V1 cortical processing remained intact.Stimuli processed by the intact V1 were able to induce similar amounts of conditioned anticipatory licking to that observed prior to the SC being inactivated. Similarly, visual CSs evoked responses in putative DA neurons that reflected predicted reward value. These results suggest that visual signals through V1 are sufficient to evoke classically conditioned responses and value-coded activation of midbrain DA neurons.In conjunction with our previous results, we conclude that both cortical and subcortical visual processing can independently elicit classically conditioned behavior and conditioned physiological responses in DA neurons.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Title: Astrocytic modulation of neuronal oscillations is associated with changes in cognitive flexibility

Authors: *A. T. BROCKETT, G. A. KANE, E. GOULD
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Abstract: Astrocytes are a highly heterogeneous and relatively understudied cell type. Across evolution, animals with more complex brains capable of more complex behavior also have more numerous and morphologically complex astrocytes. This suggests that astrocytes may be active participants in complex cognition. Recent evidence suggests that astrocytes in the medial prefrontal cortex (mPFC) change under conditions associated with enhanced cognitive flexibility (Brockett et al., 2015), while temporary disruption of astrocyte functioning is associated with diminished neuronal oscillations typically associated with cognitive behavior (Lee et al., 2014). Improvements in mPFC-dependent cognitive abilities such as cognitive flexibility are generally associated with changes in neuronal oscillations, particularly in the gamma and theta frequency ranges (Dajani et al., 2015). It is unclear what the cellular mechanism(s) responsible for the generation/ regulation of neuronal oscillations is, however, a recent study suggests that an astrocyte protein, S100β may be important for the regulation of rhythmic firing in neurons (Morquette et al., 2015). Few studies have examined whether manipulation of astrocyte functioning is associated with changes in cognitive flexibility and, subsequently, changes in neuronal oscillations. In order to investigate whether manipulation of astrocyte functioning alters cognitive flexibility and neuronal oscillations, we treated animals with either the drug L-alpha-aminoadipic acid (L-AAA), an astrocyte specific toxin or S100β, an astrocyte protein associated with enhanced rhythmic firing and tested rats on the attentional set-shifting task (ASST). We found that reduction of astrocyte number using L-AAA in the mPFC was associated with impaired cognitive flexibility, and conversely that infusion of S100β into the mPFC, enhanced cognitive flexibility. In a separate cohort of rats, we recorded unilateral local field potentials (LFPs) in the mPFC of rats treated bilaterally with either L-AAA or S100β. L-AAA treatment was associated with decreased power in the delta (0-4 Hz), alpha/ beta (12-20 Hz), and gamma (30-80 Hz), but not theta (6-10 Hz) frequency ranges. By contrast, infusion of S100β produced no changes in power across any frequency ranges, however, S100β infusion was associated with increased synchrony between theta and gamma oscillations, similar to what has been observed under conditions of enhanced cognitive ability. Collectively, these findings suggest that astrocyte

manipulations that alter cognitive flexibility are associated with changes in neuronal oscillations thought to be important for mPFC function.

Disclosures: **A.T. Brockett:** None. **G.A. Kane:** None. **E. Gould:** None.

Poster

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Science and Technology Commission of Shanghai Municipality 15JC1400104

Title: A recurrent neural network model of task switch cost

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Abstract: Flexible task switching based on the relevant context is a key component of executive control. When humans and animals switch from one task to another, there is commonly a “switch cost”: an increase in error rate and/or reaction time. In task-switching paradigms where one task is more difficult than the other, such as the Stroop task or the Pro/Anti orienting task, the switch-cost is often asymmetric: the switch from the hard task (e.g. color-naming or Anti-orienting) to the easy task (e.g. word-reading or Pro-orienting) induces a larger cost than the reverse switch. This counter-intuitive phenomenon has been observed in humans, monkeys, and rats, and provides strong support for the "task-set inertia" theory of switch cost: that the cost is mostly due to a temporal carryover of the previous task set (Allport et al., 1994).
Despite the prevalence and robustness of this phenomenon, the fundamental question of how such as asymmetric switch cost is developed remains unknown. To understand the source of task switch cost and its underlying mechanism, we trained recurrent neural networks (RNN) to perform the Pro/Anti task-switching behavior using the same training procedures as those described in a recent rat study (Duan et al., 2015). Specifically, we used a simple RNN with 5 input nodes, 10 hidden nodes, 3 output nodes; and random Xavier initialized connection weights. The model was trained with a supervised learning rule using the Minpy implementation of backpropagation through time (https://github.com/dmlc/minpy). After going through the shaping steps identical to those experienced by the rats, the majority of our agents demonstrated the asymmetric switch-cost phenomenon. These results argue that the switch cost and its asymmetry are properties shaped by experiences, and not constrained by specific neural circuits. Having

simulated switch cost asymmetry in our agents, we then conducted an experiment impossible to do with current neuroscience techniques: we silenced the recurrent feedback but preserved the input activity of the network. This eliminated task switch-cost, providing evidence that the memory of the previous task maintained in the internal dynamics of the network interferes with the rule on switch trials, supporting the "task-set inertia" theory.

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Poster

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Support: NIAAA 5T32AA014127

NIAAA 1P50-AA022534-01

Title: Increasing orbitofrontal coordination and restoring behavioral flexibility after prenatal alcohol exposure

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Abstract: Increasing evidence demonstrates that moderate alcohol consumption during pregnancy can have negative impacts on executive function including attention, working memory and behavioral flexibility. We have previously shown that moderate prenatal alcohol exposure (PAE) in the mouse via a drinking in the dark paradigm impairs executive function by significantly increasing perseverative responding on a touchscreen visual reversal-learning task. Single unit and local field potential (LFP) recording during task performance found that moderate PAE mice had significantly decreased coordinated activity in the orbitofrontal cortex (OFC) after correct responses during early reversal. This loss of OFC LFP coherence was accompanied by decreased synchrony between the OFC and the dorsal striatum (dS). In the current studies, we investigated whether precise stimulation of the OFC pyramidal neurons or OFC-dS projection neurons following choice would 1) reintroduce OFC coherent activity lost in PAE mice and 2) reduce PAE induced maladaptive perseveration and increase behavioral flexibility. PAE (10% EtOH available 4 hours every day, throughout gestation; BAC: ~90mg/dL) and control mice from dams who drank saccharine only (SAC) were obtained from the NMARC Scientific Core. Mice were trained through discrimination and then microinfused with channelrhodopsin-expressing lentivirus (α-CAMKII-ChR2(H134R)-EYFP) directly into the OFC

or retrograde expressing herpesvirus (hEF1α-hChR2(H134R)-mCherry) into the dS. Mice were then implanted with recording optrodes that allowed single-unit and LFP recording of OFC and dS and light stimulation of OFC. Four weeks post-injection, PAE and SAC mice were tested to ensure discrimination learning retention and then tested on the reversal. During reversal session 1, 3, and 4, where PAE mice are shown to be significantly more perseverative, PAE and SAC mice received light pulses (10 Hz, 5mW, 5ms pulse for 1s) or no stimulation 1 second following a correct choice while waveform and LFP activity was recorded. We found that optogenetic stimulation was able to increase OFC firing *in vivo* and alter coordinated activity following correct choices during reversal. Targeted stimulation during early reversal also reduced perseveration in PAE mice compared to non-stimulated controls. These data provide evidence that stimulation of specific populations of cortical neurons may aid in value updating and reduce the impaired flexibility seen after PAE.

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Support: SIP 20161359

Title: Maternal fructose intake during pregnancy and lactation reduces learning capability in adult offspring

Authors: *F. A. TOBAR, S. R. ZAMUDIO, Sr, L. QUEVEDO, Sr
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Abstract: Fructose is a monosaccharide present naturally in fruits, vegetables and honey. Due to its high sweetness and low cost, fructose use and consume has increased significantly in the last few decades, which has resulted in an increased risk in the development of various metabolic disorders, as obesity, dyslipidemia, insulin resistance and type II diabetes. Experiments in adult rats have shown that fructose consumption induces metabolic changes and reduces synaptic plasticity in hippocampus and cognitive performance. Several studies have demonstrated a significant relationship between maternal fructose intake and metabolic disorders in their offspring. However, there is less evidence about the long-term effects of fructose intake on the cognitive performances in adult offspring. Therefore, a study to evaluate the long-term effects of fructose intake on the metabolism and behavior in adulthood of offspring of dam rats fed a high-fructose diet was performed. Virgin female Sprague-Dawley rats (210-230) were divided into two groups: control group fed with regular diet and fructose group with high-fructose diet (50%

w/w), both groups were fed whit their respective diets during gestation and lactation stages. A tendency to higher body weight in offspring of fructose group compared with control group at postnatal day 60 was observed. This difference became significant on the postnatal day 100, including higher fat deposits. Results also shown a significant difference in fasting insulin, the HOMA index, in the insulin AUC and triglycerides, but not in cholesterol of adult offspring of fructose group compared with control group. In Barnes maze test, results shown that adult offspring of fructose group learn slower than adult offspring of control group. In this regard, we conclude that consumption of a high-fructose diet during gestation and lactation induces metabolic programing associated with deficits in learning process in adult offspring.

Disclosures: **F.A. Tobar:** None. **S.R. Zamudio:** None. **L. Quevedo:** None.

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Topic: H.01. Animal Cognition and Behavior

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Title: Maternal overnutrition leads to cognitive and neurochemical abnormalities in the offspring

Authors: *D. PELEG-RAIBSTEIN, C. WOLFRUM
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Abstract: Ample evidence from epidemiological studies have linked maternal obesity with metabolic disorders such as obesity, cardiovascular disease and diabetes in the next generation. Recently, it was also shown that maternal obesity has long-term effects on the progeny's central nervous system. However, very little is known as to how maternal overnutrition may affect in particular the cognitive abilities of the offspring. Here, we examined whether maternal high-fat diet (HFD) exposure in mice may induce long-term cognitive impairments and neurochemical dysfunctions in the offspring during different age trajectories: peripubertal (postnatal day 35), adult (postnatal day 70) and aged adults (postnatal day 180). We found that maternal HFD led to cognitive disabilities in adult HFD offspring compared to controls. It was mostly evident in a discrimination learning paradigm in the T-Maze task and in active avoidance learning. In contrast, working memory performance in the Y-Maze was intact. Impairments were evident in the adult aged group. In addition, adult and adult aged HFD offspring showed potentiation of prepulse inhibition (PPI). The cognitive impairments observed at adulthood were associated with attenuations of amino acid levels in the medial prefrontal cortex and the hippocampus regions of HFD offspring. These data suggest that HFD offspring are at an increased risk to develop cognitive deficits, affecting learning and memory processes in adulthood. Furthermore, maternal

HFD exposure may enhance brain aging manly in the hippocampal and prefrontal cortex structures that may explain the cognitive deficits observed in the offspring.

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706. Executive Function in Learning and Memory

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 706.21/SS55

Topic: H.01. Animal Cognition and Behavior

Support: National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2014R1A2A2A01007289)

Title: Cell penetrating fusion protein in postoperative cognitive dysfunction model

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Abstract: Impaired cognitive functioning is commonly presented after surgical operations and some patients who received surgery are vulnerable to postoperative cognitive dysfunction (POCD). Signs of POCD are closely associated with development of systemic or hippocampal inflammation. However, the precise pathophysiological mechanisms and effective therapy for POCD still remain unclear. After injury, the transcriptional factor, nuclear factor kappa (κ) B (NF-κB) is considered as a key regulator/stimulator of inflammation amplification. Therefore, here we developed cell-penetrating fusion protein called nt-p65-TMD, which inhibits NF-κB activation by translocating into nucleus efficiently, and discovered a potent role of nt-p65-TMD in surgery-induced cognitive impairment. In this study, abdominal surgery model was induced by rubbing intestine and clamping superior mesenteric artery in ICR adult mice. We evaluated behavioral parameters related to cognition and memory functions after nt-p65-TMD treatment by elevated plus maze, novel object recognition test, and passive avoidance test. We assessed vascular integrity impairment and immune cell recruitment in the brain, and inflammatory and anti-inflammatory mediator levels in the spleen and hippocampus. Also, inflammatory and anti-inflammatory mediator levels were measured in cultured microglia and macrophage cell line after treatment nt-p65-TMD under LPS challenge. Our data showed that the nt-p65-TMD has strong immune-regulatory properties to reverse surgery-induced increment of cerebrovascular integrity impairment, subsequent peripheral immune cell infiltration and inflammation amplification, which can lead to decline cognition. Especially, nt-p65-TMD has a novel function to regulate systemic inflammation toward anti-inflammatory environments. Conclusively, nt-p65-TMD will be of great significance in the treatment of POCD.

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Poster

706. Executive Function in Learning and Memory

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 706.22/SS56

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R21 CA183736

Title: Nasal administration of mesenchymal stem cells promote recovery from cisplatin-induced chemobrain

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Abstract: Chemotherapy-induced cognitive impairment (CICI), termed “chemobrain”, is a common neurotoxic side effect of cancer treatment and significantly reduces patient’s quality of life. We explored the possibility of treating chemobrain by nasal administration of bone-marrow derived mesenchymal stem cells (MSC). Male C57BL/6J mice were injected with cisplatin for two 5-day cycles followed by nasal administration of murine MSC at 48- and 96-hours after cisplatin treatment. Cisplatin- induced deficits in executive functioning and working memory were assessed by the puzzle box test, novel object/place recognition test, and the Y-maze. Nasal MSC administration promoted recovery from CICI, as shown by a reversal of the deficit in executive functioning and of working memory. Cisplatin-treated mice showed lower global efficiency of the functional connectome compared to sham controls as determined by resting-state functional magnetic resonance imaging (rs-fMRI). However, MSC-treated animals showed similar global efficiency to sham controls. On the cellular level, cisplatin treatment resulted in a synaptosomal mitochondrial dysfunction, whereas nasal MSC were capable of promoting full recovery of mitochondrial function. Our data support the hypothesis that nasal administration of MSC promote recovery from chemotherapy-induced cognitive deficits, and restore decreased global efficiency of neuronal connectivity and synaptosomal mitochondrial dysfunction. Nasal MSC treatment may thus offer a realistic treatment for chemobrain.

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Poster

707. Learning: From Model Systems to Modeling

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Topic: H.01. Animal Cognition and Behavior

Support: Canadian Institutes of Health Research

Natural Sciences and Engineering Research Council

Title: Lateral prefrontal cortex single neuron and ensemble activity during associative learning in virtually navigating monkeys

Authors: *L. DUONG[1], R. A. GULLI[2], B. W. CORRIGAN[3], M. L. LEAVITT[3], G. DOUCET[4], J. C. MARTINEZ-TRUJILLO[5]
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Abstract: Associative learning and memory is imperative to our cognition and informed decision making. This essential function is mediated by coordinated activity across several brain areas. In primates, the lateral prefrontal cortex (PFC) and the hippocampus are highly coordinated during associative learning (Brincat & Miller, 2015). Changes in single neuron activity in dorsolateral PFC correlate with changes in behavioral performance during associative learning tasks (Asaad et al., 1998) and rule context (Rainer et al., 1998), corroborating primate dlPFC lesion studies resulting in impaired performance on associative learning tasks (Petrides,1987). However, little is known about how prefrontal single neuron activity and ensemble interactions support associative learning. To study this, we recorded ensembles of extracellular spiking activity from two male macaque monkeys performing a novel joystick task in a 3D virtual X-shaped maze (Doucet et al. 2016), incorporating elements of learning, and spatial navigation in a naturalistic environment with unconstrained navigation and eye movement.
Our task was a classical A-B-A block design wherein both blocks A and B of each session contained a context-object associative learning task. In both blocks, monkeys used a joystick to freely navigate through the maze towards a branched decision point. The monkeys then chose to navigate towards one of two colored discs, with the correct disc being contingent on the texture of the maze walls (context: wood or steel). In block A trials, the context-object association was fixed across all sessions (wood context, purple>orange; steel context, orange>purple). In block B

trials, a novel pair of colored discs were presented, and monkeys learned the new context-object association by trial-and-error. This bookended block design allowed us to compare the consolidated neural state during block A trials against the learning states during block B. We recorded neural activity from two chronically implanted multielectrode arrays in the left dorsolateral and ventrolateral prefrontal cortex of macaque monkeys while they performed the task.
We regressed animal behavioural and experimental parameters onto single unit trial activity during block A (consolidated state) and B (learning state), and found an emergence of tuning for various task parameters. Furthermore, we then analyzed ensemble interactions and temporal dynamics on a trial-by-trial basis, and found striking differences between consolidated and learning trajectories in state-space. Taken together, our findings show the complexity of PFC single neuron and ensemble activity during associative learning.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NSERC

CIHR

Title: Hippocampal single neuron and ensemble activity during associative learning in virtually navigating primates

Authors: *R. A. GULLI[1], L. DUONG[2], B. W. CORRIGAN[3], G. DOUCET[4], M. L. LEAVITT[5], S. WILLIAMS[6], J. C. MARTINEZ-TRUJILLO[3]
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Abstract: The hippocampus has long been studied as a component of two functional systems in the brain: cognitive mapping of the sensory environment, and memory (O'Keefe and Nadel, 1978; Buzsaki and Moser, 2013; Eichenbaum and Cohen, 2014; Schiller et al., 2015). How neurons in the hippocampus could simultaneously support these diverse cognitive functions is unclear. To determine whether these functions are simultaneously supported by a common or

distinct neural substrate within the hippocampus, we recorded single-neuron spikes from the hippocampus of two rhesus monkeys (Macaca mulatta) while they performed two tasks in the same virtual reality environment (VE): 1) foraging; and 2) a context-object associative learning (AL) task.
In the foraging task, animals navigated through the VE towards a red volume randomly positioned in the maze (https://youtu.be/aWvheMzxMJo). In the AL task, monkeys learned a reversed two-context, three-object reward value hierarchy embedded into the VE (https://youtu.be/RHx9Lw65oDw). The context was defined by the texture of the walls of the maze, and these were fixed across days. The context and object pair on every trial was selected randomly, and new object colors were pseudo-randomly selected daily from a seven-color set; thus, a new associative hierarchy was learned daily.
In both tasks, place fields of hippocampal neurons cover the entire maze, and this activity can be used to decode the subject's position in the maze. Spatial decoding improves when accounting for heading direction in the maze, and furthermore when decoding gaze position in the environment rather than subject position. However, in all cases, these "cognitive maps" do not generalize across tasks, even though the environment is unchanged. Changes in the cross-task neural code are attributed to encoding of attended features of the associative learning task in single neurons: namely neurons encoding the texture of the walls, the colored objects, and the conjunction of these two in the AL task. The development of these selectivities mirrors the subjects' learning in the AL task.
This work suggests that the hippocampus does not strictly encode sensory maps to guide survey navigation. Instead of framing the hippocampus as the brain's Geographical Positional System, the flexible representations observed here reflect the mnemonic processes inherent in a General Processing System (Tulving, 1985). Hippocampal neurons may provide a substrate for rapid encoding behaviorally relevant associations in a context dependent manner. These representations may be consolidated in neocortex, including but not limited to prefrontal cortex (see, Duong, Gulli, et al., SfN 2017).

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: CIHR

NSERC

Title: Prefrontal cortex ensemble activity during associative visuomotor rule learning in primates

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Abstract: Lateral prefrontal cortex (LPFC) is necessary for learning associations between arbitrary pairs of stimuli and responses. Lesions to LPFC area 8a severely impair the ability of macaques to learn associations between more than one stimulus-response pair simultaneously (Petrides, 1987). Saccade direction selectivity in single LPFC neurons has also been shown to emerge earlier in a trial as macaques learn the associations between objects and saccade directions (Asaad et al., 1998). However, the ensemble-level mechanisms of conditional associative learning in macaques remain poorly understood. The need to average neuronal activity across multiple instances of learning in single neuron recordings can mask the underlying neuronal dynamics. In order to investigate this issue, we recorded from microelectrode arrays implanted in macaque area 8a while subjects learned pairs of conditional visuomotor associations.
We trained two monkeys to perform the following task: First, a rule was generated at the beginning of a recording session. Two of three possible color cues were randomly chosen, and one of four possible pairs of target locations were also randomly chosen. Each color was associated with one of the targets, for example blue = top target, green = bottom target. A single trial started with central fixation (700ms), then presentation of the two targets (250-500ms), presentation of one of the two colors cues (1000ms), removal of the color cue and a delay epoch (300ms), and extinguishing of the fixation point, cueing the animal to make a saccade to one of the targets. If they chose the target associated with the color cue, they received a juice reward. Trials were repeated until the animal reached criterion, which we defined as two blocks of 30 trials with at $\geq$ 80% success. After reaching criterion, a new rule was generated by randomly sampling, with replacement, from the pool of cue colors and target locations.
Animals performed 2-10 rule switches in a single recording session. We used a linear classifier to decode ensemble activity, and found that saccade direction decoding was more robust after compared to before learning; this difference emerges roughly 500ms after presentation of the color cue and persists throughout the remainder of a trial. We also found that decoding performance during the final 200ms of the delay epoch correlates with instantaneous measures of behavioral performance (median $\rho = 0.75$).
Our results indicate that ensemble representation of saccade direction is stronger after learning, and that the robustness of ensemble saccade representation correlates with learning-related fluctuations in behavioral performance.

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Poster

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Support: CIHR Grant MOP-102482

Title: The macaque fronto-striatal-hippocampus axis encodes feature-specific prediction errors

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Abstract: When only one stimulus feature among many predicts reward, it is pivotal for an agent to learn which specific feature is causally linked to changes in reward outcomes. This linkage could be achieved through feature-specific prediction error (PE) signals, but it is unknown where these feature-tuned PEs might be encoded and whether PE signals carry sufficiently detailed feature information to serve as selective learning signals for updating synaptic weights. To find feature-specific PEs, we combined data from neuronal recordings in anterior cingulate cortex (ACC), dorsal prefrontal cortex (PFC) and hippocampus (HPC) of two macaques, and of ACC, PFC, caudate nucleus (CD) and ventral striatum (VS) of one macaque. All animals performed one of two variants of a feature-based reversal learning task. The task presented, peripherally to the gaze center, two moving gratings that differed in color, location, and motion. In one task variant, animals reported the rotation of the grating, in the second variant, the motion direction of the grating with the reward-associated color, respectively. The rewarded color was reversed uncued between blocks, with rotation/motion direction and location varying independently of color. PEs were quantified using a reinforcement learning model with Bayesian feature-weighting. Neurons were identified as encoding positive (pPEs), negative (nPEs) or absolute (unsigned PE) prediction errors when their firing rate correlated with the magnitude of the PE. PE signals were identified as feature-specific when they were selectively larger for e.g. a specific rewarded color. We found that on average 55% of all neurons encoded a PE signal. For 85% of those neurons the PE signal was selective for the feature giving rise to the PE. These feature-specific PEs (1) were found in all areas tested, (2) were more strongly encoded than nonspecific PEs, and (3) for pPEs were most often specific to the reward-associated color dimension. Feature-specific PEs were consistently encoded earliest in the HPC and latest in VS. These results document that across the entire fronto-striatal-hippocampus axis, prediction error encoding is tuned to the features that give rise to the PEs. The latency analysis suggests that the HPC plays an essential role in identifying which sensory features give rise to unexpected outcomes. We speculate that the feature specificity of the error signals allows to identify those

synapses across the network that need updating during learning, enabling selective credit assignment in feature space.

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Poster

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Support: NIH Grant P20 GM103645

Tosteson Fellowship

Neurosurgery Research and Education Foundation Young Clinician Investigator Award

Title: Assigning credit : Sustained neural activity between prefrontal cortex and striatum

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Abstract: Selecting an action to achieve a desired outcome in response to a conditional stimulus requires learned stimulus-action-outcome mappings. However, if the causal features are separated in time or intermingled with distractors, how does the neural activity provide a stable, cross-temporal representation? This is the credit assignment problem. We designed a task in which two non-human primates performed a credit assignment task. We recorded multiple single neurons in the lateral prefrontal cortex and dorsal striatum simultaneously. Here, we mainly focused on analyzing prefrontal-striatal interactions. We observed sustained neural activity across the prefrontal cortex and striatum beginning with feedback but extending well past this. This sustained, feedback-triggered activity may contribute to credit assignment.

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Poster

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Support: Postbaccalaureate Research Education Program (R25GM064118)

Ichan School of Medicine at Mount Sinai Seed Fund

Title: Structural changes in the primate brain following cognitive training

Authors: *J. SIMON, IV[1], C. G. DAMATAC[1], J. OLMSTEAD[2], J. NAGY[1], S. FROUDIST-WALSH[1], D. L. DICKSTEIN[3], M. VARGHESE[1], W. G. JANSSEN[1], L. FLEYSHER[2], R. O'HALLORAN[2], P. L. CROXSON[1]
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Abstract: Background:
Cognitive training therapy has been used to assist in recovery after loss of function. However, how long these interventions last and the underlying neuronal dynamics remain unknown. We investigated this using MRI measures of structural change and microstructural measures of neuron morphology. We hypothesized that training monkeys on an object recognition memory task that depends on the ventrolateral prefrontal cortex (VLPFC) would lead to volumetric increases in grey matter that would have specific microstructural correlates.
Methods:
We injected pyramidal neurons from layers 2/3 of the VLPFC and a control region, perirhinal cortex (PRh) via electric current (10nA) with Lucifer Yellow dye. Neurons were traced in Neurolucida at 40x. We performed Sholl analysis of traced neurons with concentric circles every 30um. We also analyzed high resolution z-stack images of dendritic segments (63x magnification approximately 50-100um away from the soma) for spine characteristics.
Results:
Monkeys learning the VLPFC-dependent task showed increases in grey matter volume selectively in VLPFC compared with control monkeys. Sholl analysis revealed increased basal dendritic branching complexity in the VLPFC. This finding was reversed in the PRh, which displayed increased basal dendritic branching complexity in the control monkeys, which learned a version of the task dependent on PRh. There was also a group difference for spine density, apical head diameter and spine volume.
Conclusions:
Cognitive training resulted in dynamic long-lasting changes that can be measured with both MRI

and microstructural measures of dendritic arborization and spine growth. This is the first study of this relationship in non-human primates.

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Poster

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NSF-GRFP DGE-1444932

Title: Impaired cognitive flexibility after neonatal perirhinal lesions in rhesus macaques

Authors: ***A. R. WEISS**[1,2], J. B. WHITE[2], R. RICHARDSON[2], J. BACHEVALIER[2]
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Abstract: Previous research showed that monkeys with neonatal perirhinal lesions (Neo-PRh) were impaired on working memory tasks that generated proactive interference, but performed normally on working memory tasks devoid of interference (Weiss et al., 2016, Front Sys Neurosci, 9:179), suggesting that working memory processes were spared after the Neo-PRh lesions. However, these findings also showed that Neo-PRh lesions may have disrupted cognitive processes important for resolving proactive interference, such as behavioral inhibition and/or cognitive flexibility. For example, increases in perseverative errors observed in the Neo-PRh animals could be due to failure to suppress the influence of previously acquired stimulus-reward associations (behavioral inhibition), resulting in repetitive tendencies. However, a second interpretation is that the impairment could be due to difficulty shifting attention towards new stimulus-reward associations (cognitive flexibility), resulting in a tendency to choose the previously rewarded stimulus. Lesion studies in monkeys have already demonstrated a double-dissociation between behavioral inhibition supported by the orbitofrontal cortex (OFC), and cognitive flexibility supported by the ventrolateral prefrontal cortex (vlPFC) (Dias et al., 1997, J Neurosci, 17:9285). Given that the PRh has interconnections with both of these cortical areas (Suzuki, 1996, Op Neurobiol, 6:179), it is possible that the PRh also may play a role in mechanisms underlying behavioral inhibition and/or cognitive flexibility. To distinguish between these two possible explanations, we characterized the ability of the same Neo-PRh monkeys to

perform a task that taps both capacities: the Intradimensional-Extradimensional set-shifting paradigm. The results indicated that Neo-PRh monkeys completed the simple and compound discrimination stages, the intradimensional shift stage, and all reversal stages (measuring behavioral inhibition) comparably to controls, but made significantly more errors on the extradimensional shift stage of the task (measuring cognitive flexibility) as compared to age- and experience-matched controls [t(9)=-2.320, p=0.045]. These data demonstrate that impaired cognitive flexibility is the likely source of increased perseverative errors made by the same Neo-PRh monkeys when performing WM tasks, rather than impaired behavioral inhibition, and imply that the perirhinal cortex may play a unique and critical role in the development of attentional set shifting abilities supported by the vlPFC. This work was supported by grants MH-58846 and NSF-GRFP DGE-1444932.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: 5R01MH099505-05

Title: Transient inactivation of the parahippocampal cortex impairs nonnavigational spatial memory in macaques

Authors: *E. LAFLAMME[1], H. WAGUESPACK[2], P. A. FORCELLI[3], L. MALKOVA[4]
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Abstract: Our lab has previously reported that transient pharmacological inactivation of the hippocampus severely disrupts performance on the Hamilton Search Task (HST), a self-ordered non-navigational test of spatial memory (Forcelli *et al.*, 2014). In this task animals are presented with an array of eight boxes, each containing a food reinforcer; one box may be opened per trial, with trials separated by a delay. Only the spatial location of the boxes serves as a cue to solve the task. The optimal strategy is to open each box once without returning to previously visited locations. Following hippocampal inactivation animals performed at chance levels on 30 sec delay trials. In accordance with the dorsal-ventral stream hypothesis (Ungerleider & Mishkin, 1982), spatial information enters the hippocampus through a relay in the parahippocampal cortex (PHC). Here, we hypothesized that inactivation of the PHC would thus disrupt memory

performance on the task. Three male rhesus macaques (*Macaca mulatta*) were pre-trained on the HST prior to implantation of an MRI-guided stereotaxic microinfusion platform. Subject Y received seven bilateral microinfusions of the glutamatergic antagonist kynurenic acid (KYNA, 100mM, 1.5µl) and six of physiological saline (1.5µl) in the PHC; subject L received seven bilateral microinfusions of KYNA (100mM, 1.5µl) and four of saline (1.5µl); and microinfusions for subject S are under way. The preliminary data demonstrate that transient inactivation of the PHC impairs HST performance in comparison to saline controls. The number of trials to complete the task and the repetition index (a measure of the frequency and severity of opening errors) fell to chance levels. It did not impair performance on a variation of the HST which has color cues in addition to spatial cues, providing the option of a non-spatial strategy. This finding is consistent with our previous data showing impairment after hippocampal inactivation.

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Topic: H.01. Animal Cognition and Behavior

Support: FIRB 2010

Title: Mapped or to be mapped? Learning the meaning of new stimuli increase the cross-correlated activity of prefrontal neurons

Authors: *S. NOUGARET, L. FERRUCCI, E. MARCOS, A. GENOVESIO
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Abstract: To face of new situations, animals have to learn the appropriate behavior and reduce the number of unproductive choices to be the most effective in no time. The prefrontal cortex is assumed to be a key component in such a learning implying that each new association must be represented at its neuronal level. Nevertheless, whether and how this signal is encoded by the prefrontal cell-assemblies in not clear. In the present study, to better understand this mechanism we analyzed the correlated firing of simultaneously recorded pairs of neurons and the variability of their firing rate in the dorsolateral and the mediolateral part of the prefrontal cortex of two rhesus monkeys performing a conditional motor tasks in which three stimuli should be associated to three spatial targets with either new (new mapping task) or familiar associations (familiar mapping task). In this tasks after a period of fixation, a visual instruction stimulus appeared at that location, and three potential response targets appeared in three positions: right, left, and up from center. One stimulus was selected in each trial from a set of three and the disappearance of

the stimulus served as the go signal for the saccade to one target. Each stimulus was mapped to only one response. The only difference between these two tasks was that in one case, the mapping between stimuli and targets was new and required learning while in the other case was already acquired previously. Of the 422 simultaneously recorded pairs of neurons, we found a higher number of neural pairs significantly correlated during stimulus presentation in the new mapping task (38/422, 9%) than during the presentation of stimuli in the familiar mapping task (16/422, 4%) (2-sample χ^2 test, $p < 0.01$). Moreover, during the same epoch, the variability of the firing rate of these prefrontal neurons was significantly higher in the new mapping task than in the familiar mapping task (Fano factor, 2.1 vs 1.8, paired t test, $p < 0.001$). These results demonstrate that the correlation structure and the variability represent major components of the learning processes of conditional motor associations in the prefrontal cortex.

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Title: Learning sound sequences in mouse auditory cortex

Authors: *A. G. LIBBY[1], T. BUSCHMAN[1,2]
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Abstract: Making accurate predictions is a core cognitive function: by predicting upcoming events, we can respond faster and optimize our actions. Our ability to make predictions relies on implicitly learning the common statistical relationships in our environment. However, the circuit mechanisms that allow the brain to learn these regularities remain unknown. To study how associations are learned locally at the sensory level, we performed chronic electrophysiological recordings in mouse auditory cortex, while they repeatedly listened to a sequence of chords: a common chord sequence (A-B-C-D) and an uncommon sequence (A-B-C*-D). To probe the extent to which an association within the sequence is learned, we morphed the 3rd sequence element between the common (C) and uncommon (C*) chords. Using data from multiple channels within auditory cortex, we built a classifier to track how the information within the neural responses changes during repeated experiences with the common sequence. We find shifts in the neural responses to mixtures of C and C*after learning. Specifically, the neural responses

to C* increasingly match the response to C. This suggests exposure to statistical relationships changes the organization of neural representations in early sensory cortex.

Disclosures: A.G. Libby: None. **T. Buschman:** None.

Poster

707. Learning: From Model Systems to Modeling

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 707.11/TT1

Topic: H.01. Animal Cognition and Behavior

Support: ONR AWD1004142 N00014-16-1-2085

Title: Memory through randomness: A spiking network model for flexible working memory

Authors: *F. BOUCHACOURT[1], T. BUSCHMAN[2]
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Abstract: Working memory is the cognitive ability to actively maintain information during mnemonic delays of several seconds. Importantly, working memory is extremely flexible: we are able to hold anything in mind. However, working memory is often modeled as an attractor-like persisting state of activity in the dynamics of tightly tuned sensory neurons. These models rely on carefully controlled excitatory connections between neurons, and thus are not flexible.
Here we present a novel network model that captures the flexibility of working memory. The network uses a two-layer structure combining selectively tuned neurons and randomly connected neurons. The first “sensory” layer of selective neurons encodes each input to the network. Inputs are then maintained through bi-directional recurrent connectivity between the sensory layer and the second “control” layer composed of randomly connected neurons. These interactions are sufficient to hold multiple, independent memoranda. Importantly, due to the untuned, parameter-free nature of these interactions, the model is able to maintain any type of incoming information, showing the flexibility of working memory.
In addition, this model captures several important experimental observations. First, mnemonic activity is distributed across multiple layers, as seen in human imaging and monkey electrophysiology. Second, the control layer is composed of high-dimensional mixed-selective neurons observed in prefrontal cortex. Third, the model exhibits limited capacity due to interference between representations in the control layer.
Finally, it was recently shown that the brain compensates for the capacity limitation of working memory by exploiting the statistical structure of the current task, i.e. by encoding jointly similar features of stimuli into mnemonic “chunks”. Ongoing work is investigating whether hebbian

plasticity in the network is sufficient to learn such chunks and if doing so matches behavioral improvements in mnemonic accuracy.

Disclosures: F. Bouchacourt: None. **T. Buschman:** None.

Poster

707. Learning: From Model Systems to Modeling

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Topic: H.01. Animal Cognition and Behavior

Support: NIH NEI 1DP2EY025446-01

Title: Navigating in neural and behavioral manifolds with mutli-site electrical microstimulation

Authors: *S. TAFAZOLI[1], K. LETAI[2], T. BUSCHMAN[3]
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Abstract: Electrical microstimulation is often used as a tool for mapping sensory-motor functions and studying the neuronal basis of cognition. We have recently shown that multi-site microstimulation can produce a multi-dimensional neural response. However, the relationship between dynamics of responses produced by micro stimulation and sensory stimulation is unknown. To test this, we combined simultaneous multi-electrode recordings, multi-site electrical stimulation, and visual stimulation in anesthetized mice. Electrical stimulation and recording were performed with 64-channel silicon probes placed in primary visual cortex. Using 32 channels for recording and 32 channels for stimulation allowed us to simultaneously record from small populations of single neurons while patterning stimulation at nearby sites. Electrical stimulation trials were interleaved by brief presentation of visual stimuli (drawn from the Caltech 101 database). We found that both visual and electrical stimulation can reliably elicit patterns of neural activity. Further analysis revealed that the response manifolds generated by both visual and electrical stimulation were largely overlapping. These findings suggest that electrical stimulation can produce neural dynamics close to natural sensory stimulation and provides a building block for probing complex neural dynamics and new generation of neural prosthetics.

Disclosures: S. Tafazoli: A. Employment/Salary (full or part-time):; Princeton University. **K. Letai:** None. **T. Buschman:** A. Employment/Salary (full or part-time):; Princeton University.

Poster

707. Learning: From Model Systems to Modeling

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Program#/Poster#: 707.13/TT3

Topic: H.01. Animal Cognition and Behavior

Support: ONR Grant N00014-16-1-2085

Title: Compression of information in visual working memory

Authors: *P. KOLLIAS, T. BUSCHMAN
Princeton Univ., Princeton, NJ

Abstract: Working memory has a limited capacity; the average adult can only remember ~4 items. However, what constitutes an 'item' in working memory is unknown. We argue that items are formed by grouping together representations that regularly co-occur together (Brady etAl, 2009). For example, statistical regularities between the letters 'S', 'f', and 'N' create a 'SfN' item that is easier to remember than the sum of its parts. To understand the neural mechanisms underlying such 'chunking', we trained monkeys on a visual working memory task where certain objects were chunk-able. Specifically, monkeys were presented with a sample array. After a memory delay, a single cue item was presented at fixation and subjects were required to saccade to its location in the remembered sample array. Chunk-able items were created by manipulating the relative frequency of some configurations of stimuli over others (i.e. there was statistical regularities between the locations of objects). As predicted, subjects memory performance was significantly better when displays contained such chunked items in comparison to 'unchunked' arrays (i.e. when constituent stimuli were in a different pattern). This effect was particularly true when memory load was increased, suggesting the chunked items were compressed in working memory, allowing for more information about other items to be stored. Importantly, patterns of error responses indicate that improvement in performance could not be explained by post-perceptual inference strategies. In summary, our results suggest that monkeys, as humans, can exploit statistical structure of stimuli to form compressed working memory representations.

Disclosures: P. Kollias: None. **T. Buschman:** None.

Poster

707. Learning: From Model Systems to Modeling

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Topic: H.01. Animal Cognition and Behavior

Support: Canadian Institutes of Health Research

Natural Sciences and Engineering Research Council

Title: Oscillatory neural activity for perceived and memorized representations of motion direction in the primate lateral prefrontal cortex

Authors: *M. ROUSSY[1], D. MENDOZA-HALLIDAY[4], J. C. MARTINEZ-TRUJILLO[2], L. PALANIYAPPAN[3]
[2]Physiol. and Pharmacol., [3]Biophysics and Psychiatry, [1]Univ. of Western Ontario, London, ON, Canada; [4]MIT, Cambridge, MA

Abstract: The macaque lateral prefrontal cortex (LPFC) is proposed to monitor both externally driven sensory stimuli during visual perception and internally driven mnemonic visual representations during working memory maintenance. Within this region, distinct populations of neurons have been identified to encode either mnemonic or perceived representations of motion direction. However, it remains unclear whether local networks in the LPFC generate different oscillatory activity during perceptual and mnemonic states. Here we address this matter by examining local field potential (LFP) oscillations and single unit activity during two different task conditions, contingent on either perception or working memory. We recorded neural activity from LPFC areas 8a and 46 in two male rhesus macaques while they performed two variants of a match to sample task. In all trials, the animals were presented with a sample random dot pattern moving in one of four directions. In the perceptual condition, the sample persisted during a delay period and the animal was required to match the direction of the sample to that of a test stimulus. In the mnemonic condition, the sample disappeared during the delay period which required the animal to complete the task using a mnemonic representation of the sample. We recorded LFP oscillations and computed their power spectrum during the delay periods using a multitaper method. We then calculated the proportion of explained variance (PEV) contributed by motion direction to test for direction selectivity of LFP sites during both task conditions. A significant number of LFP sites showed direction selectivity across all frequency bands during either the perceptual or mnemonic delay period. In addition, within the theta frequency band (4-8Hz), more sites expressed direction selectivity during the mnemonic state than the perceptual state. We also computed the proportion of sites that displayed selectivity for motion direction in the different frequency bands as a function of the encoding properties of simultaneously recorded neurons. During the mnemonic delay period, LFP sites containing memory encoding neurons showed

greater PEV in the theta frequency range than sites containing perceptual neurons. These findings suggest that different oscillatory phenomena characterize perceptual and mnemonic states across different LPFC sites and that these phenomena are linked to the coding properties of neurons within a given site. Future analysis will further examine the relationship between spiking activity and these oscillatory behaviors.

Disclosures: M. Roussy: None. **D. Mendoza-Halliday:** None. **J.C. Martinez-Trujillo:** None. **L. Palaniyappan:** None.

Poster

708. Focal and Brain-Wide Network Activity

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Support: Agence Nationale de la Recherche ANR-13-JSV4-0001-01

Agence Nationale de la Recherche ANR-10-IAIHU-06

NIH Grant NS096936-01A1

Brain and Behavior Foundation

Title: Structural variability across the primate brain

Authors: *P. L. CROXSON[1], S. J. FORKEL[2], L. CERLIANI[3], M. THIEBAUT DE SCHOTTEN[3]
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Abstract: A large amount of variability exists across human brains; revealed initially on a small scale by *post mortem* studies and, more recently, on a larger scale with the advent of neuroimaging . We considered that variability may be a useful index of complexity, and therefore a tool for understanding differences between species. However, whether brain variability is greater in humans and should be considered another layer of complexity when compared to other species is unknown. Here, we quantified the amount of structural variability in the cortex and white matter and compared the human and macaque monkey brain.
T1-weighted and fractional anisotropy maps were obtained from two sets of 10 adult healthy controls (5 males per set; age range 26 - 35 years) from the Human Connectome Project (HCP) after determining the optimal number of participants to build a template, and *in vivo* from 10 adult healthy rhesus macaque monkeys (*Macaca mulatta;* 6 males; age range 3 - 5 years). We used diffeormorphic deformation to produce optimal templates for each species (using Advanced

Normalization Tools (ANTs), and established the amount of inter-subject variability for T1 and FA maps using Gibbs' equation. Using the Jacobian determinant of the deformation, which is independent of brain volume, we compared these values between species, and assessed the hemispheric differences within species.
Grey matter was significantly more variable than white matter in both species. However, the human brain was not significantly more variable overall than the monkey brain. Both species overall showed distinct increased variability in specific regions, and there was a high degree of overlap between these regions and phylogenetically recent regions. Both species also showed an increased variability for the superficial white matter and lower variability for deep white matter structures.
Compared to monkeys, humans showed specifically lower variability in the anterior portion of the lateral prefrontal cortex. Humans also showed hemispheric differences in variability across a wide range of cortical regions, while monkeys showed almost no hemispheric differences apart from two regions of the parietal cortex. This is potentially one way in which evolution has led to divergence between the human and monkey.

Disclosures: P.L. Croxson: None. **S.J. Forkel:** None. **L. Cerliani:** None. **M. Thiebaut de Schotten:** None.

Poster

708. Focal and Brain-Wide Network Activity

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Support: Charles H. Revson Foundation Senior Fellowship in the Biomedical Sciences to P.L.C.

Icahn School of Medicine at Mount Sinai

BBSRC David Phillips Fellowship (BB/N019814/1) to R.B.M.

Title: Dynamic plasticity of the functional connectome is predicted by pre-lesion connectivity in the non-human primate brain

Authors: *S. FROUDIST-WALSH[1], P. G. F. BROWNING[1,2], J. J. YOUNG[1], K. L. MURPHY[3], R. B. MARS[4,5], L. FLEYSHER[1], P. CROXSON[1]
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Comparative Biol. Centre, Med. Sch., Newcastle Univ., Newcastle, United Kingdom; [4]Donders Inst., Radboud Univ., Nijmegen, Netherlands; [5]Fmrib, Univ. of Oxford, Oxford, United Kingdom

Abstract: The brain displays a remarkable ability to adapt following injury in order to recover function. However, the principles that govern which areas undergo plasticity, and when, are not well known. This is partly due the difficulty in obtaining pre-lesion MRI scans in otherwise healthy human subjects.
Here, we investigated the time-course of plasticity in monkeys after a focal neurotoxic lesion to the hippocampus using multi-modal MRI. We used a hierarchical connectivity analysis approach to analyze plastic functional connectivity changes across a range of spatial (global, cognitive and local networks) and temporal (acute and chronic) scales. We additionally acquired high-resolution structural MRI scans in order to analyse structural plasticity.
We found that widespread functional connectivity alterations occurred throughout the brain, and that timing of connectivity changes was critically dependent on connectivity with the hippocampus before the lesion. Acutely following the lesion the greatest changes occured in areas that were least functionally connected with the hippocampus, but over time this pattern reversed, indicating dynamic reorganisation. This happened despite structural damage being stable, and limited to structures directly connected with the hippocampus.
The brain responds to injury by widely increasing the connectivity between the majority of spared areas during the acute phase, before some normalisation of global connectivity during the chronic phase post injury, perhaps due a need to develop an energy-efficient brain network. The timing of connectivity changes in particular brain regions however is heavily dependent on pre-lesion connectivity with the injured brain area. This is likely to reflect the differing timescales of plastic responses occurring in areas with and without direct connections to the lesioned area, ranging from the release from synaptic inhibition (seconds to hours after lesion) to axon regeneration and sprouting (weeks to months later). Our findings shed light on the time-course of functional connectivity changes following damage in the otherwise healthy brain, and suggest a simple spatiotemporal rule governing plasticity: the more connected a brain region is to the lesioned area, the longer it will take to plastically adapt its connectivity.

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Poster

708. Focal and Brain-Wide Network Activity

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Topic: H.01. Animal Cognition and Behavior

Support: NIMH U01MH099059

Title: Unravelling the intrinsic functional boundaries of the macaque monkey cortex

Authors: T. XU[1], A. OPITZ[1,2], A. FALCHIER[2], G. LINN[2], D. ROSS[2], J. RAMIREZ[3], D. STURGEON[3], E. SULLIVAN[3], E. FECZKO[3], J. BAGLEY[3], S. COLCOMBE[2], D. FAIR[3], C. SCHROEDER[2,4], *M. P. MILHAM[1,2]
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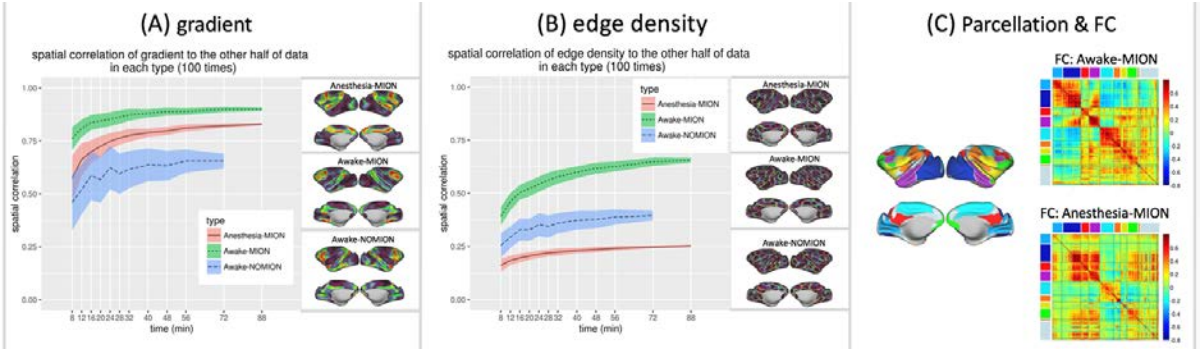
Abstract: A growing body of literature has demonstrated the ability to delineate cortical areas in the human brain based upon the detection of spatial transitions in functional connectivity (FC) profiles (Cohen et al., 2008; Wig et al., 2014). Here, we demonstrate the feasibility of extending the application of parcellation approaches to non-human primates (NHP), demonstrating the reliability of these parcellations and the distinct FC between awake and anesthetic conditions. We collected awake and anesthetized functional MRI scans from a male rhesus macaque monkey (11 sessions, 3 anesthesia sessions with MION agent [monocrystalline iron oxide particle], 5 awake sessions with MION, and 3 awake sessions without MION). We calculated FC-similarity maps, followed by the spatial gradient and edge detection computation on native surface. The spatial correlations were calculated to investigate the reproducibility and the requirement of scan time for a relatively robust boundary map for each condition. We further explored the parcel-based FC within and between network under different conditions.The overall pattern of the functional boundaries in the NHP was concordant with the measured surface geometry (e.g. strong gradients parallel to the posterior extent of the cingulate gyrus, lunate sulcus, superior temporal gyrus), though also revealed distinct characteristics (Figure 1A-B). The gradients and edge density were higher reproducibility between scans with 50 min scan data (Figure 1A-B). Strikingly, compare to awake, the FC under anesthesia exhibited decreased within- and between-networks connectivity for primary visual, sensorimotor, cingulo-opercular and frontal-parietal networks (Figure 1C).By examining the transition pattern of FC similarity in macaque under awake and anesthetic conditions, we have demonstrated the ability to detect functional boundaries using fMRI in macaque, suggesting a reliable scheme for delineating cortical organization in macaque. The unique FC patterns under awake and anesthesia provide a valuable insight into different brain states.



Disclosures: T. Xu: None. **A. Opitz:** None. **A. Falchier:** None. **G. Linn:** None. **D. Ross:** None. **J. Ramirez:** None. **D. Sturgeon:** None. **E. Sullivan:** None. **E. Feczko:** None. **J. Bagley:** None. **S. Colcombe:** None. **D. Fair:** None. **C. Schroeder:** None. **M.P. Milham:** None.

Poster

708. Focal and Brain-Wide Network Activity

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Topic: H.01. Animal Cognition and Behavior

Support: ANR-09-RPDOC-004-01

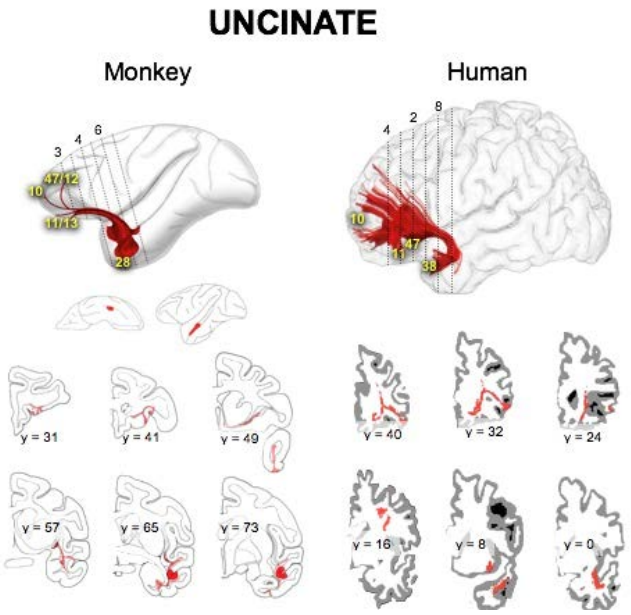
ANR-13- JSV4-0001-01

ANR-10-IAIHU-06

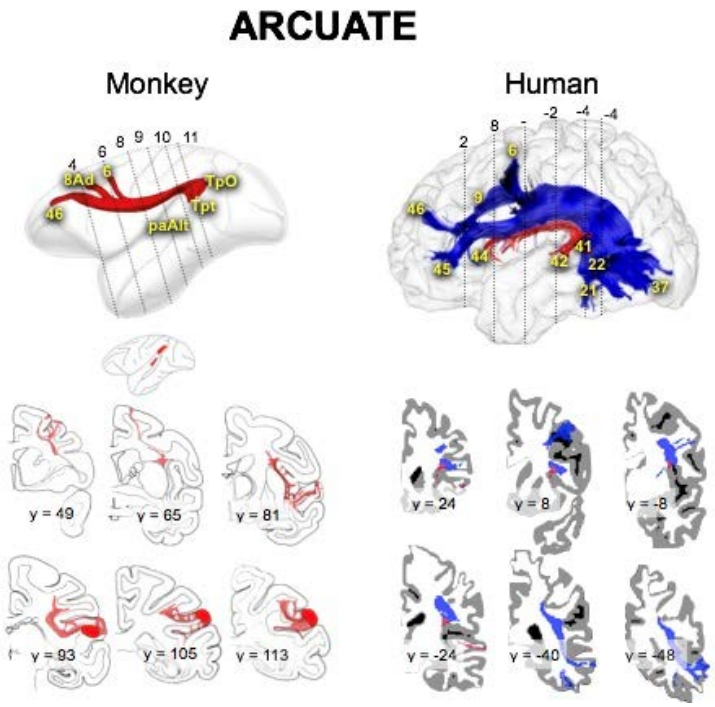
Title: Monkey to human comparative anatomy of the frontal lobe association tracts

Authors: *M. THIEBAUT DE SCHOTTEN
BCBlab, Frontlab, Inst. Du Cerveau Et La Moelle Épinièr, Paris, France

Abstract: The greater expansion of the frontal lobes along the phylogeny scale has been interpreted as the signature of evolutionary changes underlying higher cognitive abilities in humans. However, it is unknown how an increase in number of gyri, sulci and cortical areas in the frontal lobe have coincided with a parallel increase in connectivity. Here, using advanced tractography based on spherical deconvolution, we produced an atlas of human frontal association connections that we compared with axonal tracing studies of the monkey brain. For instance for the uncinate, the comparison between post-mortem axonal tracing in monkey (cases 13 and 14 modified from Schmahmann and Pandya, 2006) and human in vivo SD tractography suggests simian-human similarities.



Alternatively for the arcuate fasciculus, the comparison between post-mortem axonal tracing in monkey and human in vivo SD tractography (common anatomical features between human and monkey are reconstructed in red whereas anatomical differences have been coloured in blue) suggest ossible evolutionary changes in the connectional anatomy of the frontal lobes underlying unique human abilities such as advanced language and litteracy.



Disclosures: M. Thiebaut De Schotten: None.

Poster

708. Focal and Brain-Wide Network Activity

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Support: NIH Grant AG055556

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Title: Systematic flexibility of global functional connectivity patterns supports flexible cognitive control

Authors: *D. H. SCHULTZ, T. ITO, L. SOLOMYAK, R. CHEN, R. MILL, K. KULKARNI, M. W. COLE
CMBN, Rutgers-Newark, Newark, NJ

Abstract: Humans are highly skilled at flexibly applying previously learned rules in novel situations. Converging evidence suggests that activity in the frontoparietal control network (FPN) contributes to this ability to effectively perform novel tasks. Additionally, global patterns of functional connectivity (FC) from the FPN are highly flexible across task demands, suggesting the FPN is composed of flexible hubs. Flexible hubs are brain regions that can flexibly and rapidly alter connectivity across the entire brain depending on current task goals. We hypothesized that FC variability is an important aspect of flexible hubs that contributes to the performance of flexible control tasks. We therefore predicted that individual differences in FC variability would be correlated with individual differences in flexible control task performance. We tested this hypothesis in a large dataset (100 young adults) in which participants completed several flexible control tasks (Raven's progressive matrices, Cattell's culture fair test, Dimensional card sort, and Flanker task). Participants also completed a recently developed flexible control task called the Concrete Permuted Rule Operations (C-PRO) paradigm in the scanner. The C-PRO paradigm consists of three rule types with four variants of each type. When all of the rules are permuted it results in 64 unique rule combinations. FC was calculated for each of the 64 unique rule combinations between a standard set of regions. Consistent with our hypothesis, we found that the flexibility/variability in FPN FC patterns was greater in individuals demonstrating greater flexible control abilities. This suggests that an individual's flexible control ability is supported by the capacity of the FPN to rapidly and flexibly modify FC. We also identified regions where FC stability was related to flexible control. Stability in the FC patterns for these regions may reflect the representation of task-general information, such as "meta-task" information shared across the 64 tasks. Together these results suggest that the ability of the FPN

to flexibly yet systematically adapt functional connections is not simply a general characteristic of the network, but reflects the ability of each individual to perform tasks requiring flexible control.

Disclosures: D.H. Schultz: None. **T. Ito:** None. **L. Solomyak:** None. **R. Chen:** None. **R. Mill:** None. **K. Kulkarni:** None. **M.W. Cole:** None.

Poster

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Support: CA Prop. 63, the Mental Health Services Act and the Behavioral Health Center of Excellence at UC Davis (to EGA)

NIH grant EY13588 (to WMU)

NIH grant T32 EY015387 (to SES)

Title: The frequency-dependent dynamics of the primate frontal executive networks in a state of action preparation

Authors: *S. E. SEIDL, W. M. USREY, E. G. ANTZOULATOS, 95618
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Abstract: The cognitive control of behavior does not simply stop once the executive networks of the brain have evaluated the odds and selected an action in a context- and goal-dependent manner. Rather, even after the action has been selected, these networks must maintain a highly attentive state, in order to either carry out necessary last-moment modifications in the action plan, or to protect the action plan from interference. Successful action preparation and execution, thus, require the coordination of multiple brain networks, executive, motor, premotor and sensory. In the absence of cognitive computations, the state of action preparation offers a unique opportunity to observe the basic neurophysiological properties of the frequency-dependent coordination of large-scale executive networks. We employed techniques of multiple, spatially distributed microelectrodes in the rhesus macaque brain to record neural signals of population activity (i.e., LFPs and MUAs) from several frontal cortical and striatal regions at the same time, during action preparation. During visual fixation on a central target, a brief visual stimulus signaled to the animals the onset of a preparatory stage (preparatory cue). Following a brief and variable delay, another visual stimulus (Go cue) signaled to the animals to push a joystick for reward. Our simultaneous recordings from the caudate nucleus, anterior cingulate, dorsal

premotor, lateral and caudal prefrontal cortices revealed the temporal structure of the local network oscillations and the interactions among them. Robust changes in oscillatory power and synchrony in all these areas were predominantly concentrated in three frequency bands: the delta (1-4Hz), alpha (8-12Hz), and beta-2 (20-30Hz). Differences among the three bands were observed in (a) their trial epoch-dependence and (b) the pairs of areas they preferentially coordinated. For example, the most prominent power-changes of beta-2 were seen during the preparatory cue display, while alpha was more prominent during the preparatory delay and the inter-trial interval. In addition, the lateral prefrontal cortex was strongly synchronized with the caudate in all three bands, but synchronized with the cingulate only in the delta and alpha bands. Our data on time-frequency-dependent interactions may provide new insight into mechanisms of predictive timing and may shed light on the cooperation between the executive and motor aspects of behavioral control.

Disclosures: S.E. Seidl: None. **W.M. Usrey:** None. **E.G. Antzoulatos:** None.

Poster

708. Focal and Brain-Wide Network Activity

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Program#/Poster#: 708.07/TT11

Topic: H.01. Animal Cognition and Behavior

Title: Covert and overt face recognition, one or two routes?

Authors: *D. GÓNGORA[1], A. M. CASTRO-LAGUARDIA[1], J. IGLESIAS-FUSTER[1], E. KARAHAN[3], M. LI[3], M. VALDÉS-SOSA[1], E. GONZÁLEZ-DALMAU[2], E. GONZÁLEZ-ALEMAÑY[2], P. VALDES-SOSA[3], M. A. BOBES[1]
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Abstract: Cognitive models about face recognition postulate two independent streams of processing, one conscious involved in processing personal semantic information and another unconscious related to the affective reaction to this identity. These two streams of processing could be supported either by two parallel neural circuitries or by one single route operating in sequence. The temporal resolution of functional magnetic resonance imaging (fMRI) is too low to provide information to disentangle this matter. One strategy to overcome this issue is to reveal face information gradually in order to potentially disclose relative timing differences between different brain areas while using a very short sampling rate of BOLD acquisition. Here we adapt a paradigm from Gentile et al. (2016) to explore timing of conscious and unconscious (subliminal presentation) of familiar face processing in typical subjects. The sample was composed by 10 young healthy subjects (four females). The stimuli were unfamiliar and familiar

faces (tailored to each subject, consisting of family members or close acquaintances) of ten identities each. Face visibility was varied parametrically by creating a graded sequence of 20 images from each stimulus with decreasing degrees of phase-scrambling. The recognition threshold was determined individually as the sooner picture at which the subject was able to give the name of any person. Subliminal presentation threshold was defined as two-phase step backward of the identity's recognition threshold. We found that response latency for unconscious and unconscious familiar face processing is similar in V1 and occipital face area, whereas for face fusiform gyrus, amygdala and insula the latency is shorter for unconscious than for conscious processing. In conclusion, this support the existence of two different streams operating in parallel for familiar face processing.

Disclosures: D. Góngora: None. **A.M. Castro-Laguardia:** None. **J. Iglesias-Fuster:** None. **E. Karahan:** None. **M. Li:** None. **M. Valdés-Sosa:** None. **E. González-Dalmau:** None. **E. González-Alemañy:** None. **P. Valdes-Sosa:** None. **M.A. Bobes:** None.

Poster

708. Focal and Brain-Wide Network Activity

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Support: Canadian Institutes of Health Research

Natural Sciences and Engineering Research Council of Canada

Title: Stable representations in the prefrontal cortex of unrestrained monkeys: Linking neurophysiology to causal evidence from lesion studies

Authors: *S. TREMBLAY, C. TESTARD, M. PETRIDES
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Abstract: In the study of the primate caudal lateral prefrontal cortex (area 8A), there is a discrepancy between what has been demonstrated causally in lesion studies and what has been observed using single-neuron recordings in monkeys. Neurophysiologists using standard visual-saccadic paradigms have mostly described neurons encoding visual-attention and eye movement signals in this area. However, we know from lesion studies that bilateral ablation of area 8A produces no deficits in visual attention nor in eye movement control. In fact, bilateral lesions of area 8A result only in a specific impairment in using "if-then" instructional cues to select visual objects from the environment. We believe that this discrepancy between neuropsychological (i.e. lesion) and neurophysiological evidence is the result of the low ecological validity of standard visual-saccadic paradigms ubiquitous in monkey neurophysiology. Although these paradigms are

useful to study visual areas of the brain, we posit that they offer a limited portrait of higher-order associative areas such as the prefrontal cortex. In the current study, we introduce a new paradigm that combines multi-electrode neurophysiology in monkeys with ecologically valid cognitive testing. By performing intracranial multi-electrode recordings in monkeys that are unrestrained in their head, eye and arm movements, we show that neural ensemble activity in area 8A encodes the cognitive process predicted by lesion studies (i.e. conditional visual selection; accuracy >90%). Importantly, we show that this cognitive representation is stable even while the monkey is freely moving and looking around. We hope that this paradigm will provide a more accurate portrait of the neuronal properties of associative areas and help close the gap between neuropsychological and neurophysiological studies of the primate prefrontal cortex.

Disclosures: S. Tremblay: None. **C. Testard:** None. **M. Petrides:** None.

Poster

708. Focal and Brain-Wide Network Activity

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 708.09/TT13

Topic: H.01. Animal Cognition and Behavior

Support: DIRP/NIMH/NIH

Title: Impact of noise correlations on information scaling in large neural ensembles from the macaque prefrontal cortex

Authors: *R. BARTOLO, R. C. SAUNDERS, P. G. BROWNING, A. R. MITZ, B. B. AVERBECK
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Abstract: Characterizing information scaling in large populations of neurons has been difficult due to technical limitations in recording large numbers (hundreds) of neurons simultaneously from awake, behaving animals. Multi-electrode recording techniques have recently made such large scale recordings possible. We recorded single and multiunit activity using multi-electrode arrays (8 X 96 = 768 channels) implanted bilaterally in the prefrontal cortex (PFC) of macaques (Macaca mulatta). We were able to isolate hundreds of neurons (>500) during the execution of an oculomotor saccade task, maintaining the isolations for a large number of trials (>1500 trials). The animals were required to fixate centrally, then saccade towards a target (randomly presented either to the left or right) to obtain rewards. We were interested in estimating information scaling with ensemble size, as many theoretical models have suggested that information saturates in large neuronal populations. In addition, we studied the effect of the time bin length on information scaling. Therefore, we selected multiple random subsets of neurons of a range of population sizes within a recording session (25-700 units) and estimated information in each

subset. Spike counts within a time bin after stimulus onset were used to train a generalized linear model to predict saccade direction. First, 90% of the trials (randomized), 5% of trials were used to stop the training (early stopping regularization) and the remaining 5% were used for decoding. We further projected population activity on the linear decision boundary, and used the distribution of projected data to estimate d-prime as an information measure. We repeated this procedure using time bins of varying length (16-500 ms). We show that decoding accuracy rapidly increased as a function of ensemble size, and was nearly perfect for ensembles with more than 150 neurons. On the other hand, d-prime continued increasing with ensemble size. We then fitted nonlinear functions to the d-prime data to estimate the asymptotic value. Both the asymptotic value and the measured d-prime increase as a function of the length of the time bin, reach a peak, and then decrease. As expected, we observed that noise correlation increases as a function of time bin length. Altogether, our findings suggest an optimal time resolution that maximizes the information in the neural ensemble and minimizes the impact of correlated noise and raises questions about how this information is read-out in the brain.

Disclosures: R. Bartolo: None. **R.C. Saunders:** None. **P.G. Browning:** None. **A.R. Mitz:** None. **B.B. Averbeck:** None.

Poster

708. Focal and Brain-Wide Network Activity

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: NIH/NINDS Grant NS023945

Title: Contribution of the basal forebrain cholinergic system to cortico-cortical network interactions

Authors: *P. GOMBKOTO, M. GIELOW, C. CHAVEZ, L. ZABORSZKY
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Abstract: The basalo-cortical projection system has a complex topographic organization consisting of segregated and overlapping pools of projection neurons. The measure of overlap is related to the degree of connectivity between the cortical target of projection populations, suggesting that the organization of projections from the basal forebrain (BF) to cortical regions reflects cortico-cortical connectivity patterns (Zaborszky et al., 2015). In this study we investigated the functional circuitry between specific locations in the BF, orbitofrontal (VO/VL) and visual cortex (V2) in a visual discrimination task, in transgenic ChAT-Cre rats using high-density electrophysiology recording. Extracellular spikes were recorded simultaneously using 64-contact silicon probes chronically implanted in the BF. In addition, two 32-contact silicon

probes were implanted in the VO/VL and the V2 cortex. These cortical areas are presumed to receive strong projections from the BF regions that we targeted with our optrodes. Cholinergic neurons were optogenetically tagged by laser stimulation (10ms, <5mW) after the behavioral experimental period but within the same recording session. Functional connectivity was examined based on short-latency temporal interactions of excitatory and inhibitory neurons using a spike jittering cross-correlation method. The oscillatory pattern of cortical areas modulated by cholinergic and non-cholinergic input was calculated using spike-triggered averaged LFPs. To detect behavior dependent coherence events, we computed the probability of high coherence ($r > 0.7$) values using continuous wavelet coherences between specific BF and V2-VO/VL contact sites that show specific probability changes between different behavior epochs, including visual stimulus detection, decision making, and approach to food reward. During cholinergic activation, the cortico-cortical coherence increased at alpha and gamma bands, however beta band coherence decreased at the same locations. The dense recording sites on silicon-based recording probes in combination with optogenetic tagging of cholinergic neurons can help to disentangle the contribution of the cholinergic system to coordinate functionally related cortical areas.

Disclosures: **P. Gombkoto:** None. **M. Gielow:** None. **C. Chavez:** None. **L. Zaborszky:** None.

Poster

708. Focal and Brain-Wide Network Activity

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: Spanish MINECO BFU2012-34838

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Spanish MINECO RYC-2015-17236

European Regional Development Fund

Title: Persistent neurons drive stable population-level working memory representations

Authors: K. WIMMER[1], J. M. BARBOSA[2], A. GALÁN[2], C. CONSTANTINIDIS[3], G. MONGILLO[4], *A. COMPTE[2]
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Abstract: Neurophysiological experiments in primates have found that during the delay period of working memory tasks, a fraction of neurons in the prefrontal cortex carry information about

the stimulus as sustained activity, therefore supporting a stable code during the whole delay period. However, many neurons show strong temporal dynamics, which has given rise to the dynamic coding model for working memory. This model proposes that due to the time-varying dynamics of single neurons, a stable memory representation can only be achieved at the population level through a linear combination of individual neural responses of a sufficiently large population of neurons.

Here we set out to investigate how prefrontal neurons with different delay-period dynamics contribute to population dynamics during an oculomotor delayed-response task (Constantinidis et al. 2001). We first characterized the delay dynamics of single neurons based on their firing rate autocorrelation. Autocorrelation decays were heterogeneous, ranging from persistent neurons with slow decay to dynamic neurons with more transient delay activity autocorrelation. We tested if these neurons contributed differently to delay coding by running PCA on pseudo-population responses constructed from the *persistent* and *dynamic* neurons, respectively. Extending the result of (Murray et al. 2016), we found that the *persistent* neurons alone are sufficient to span a stable, low-dimensional mnemonic subspace and that such a subspace representation was not apparent for the population of *dynamic* neurons. Finally, we used linear decoders on small neuronal ensembles from these two putative subpopulations (*persistent* and *dynamic*) and compared stimulus information during different time points throughout the whole trial period. Persistent neurons carried more information on any tested time point.

In sum, we conclude that persistent neurons are the main drivers of memory-selective delay period dynamics in our data.

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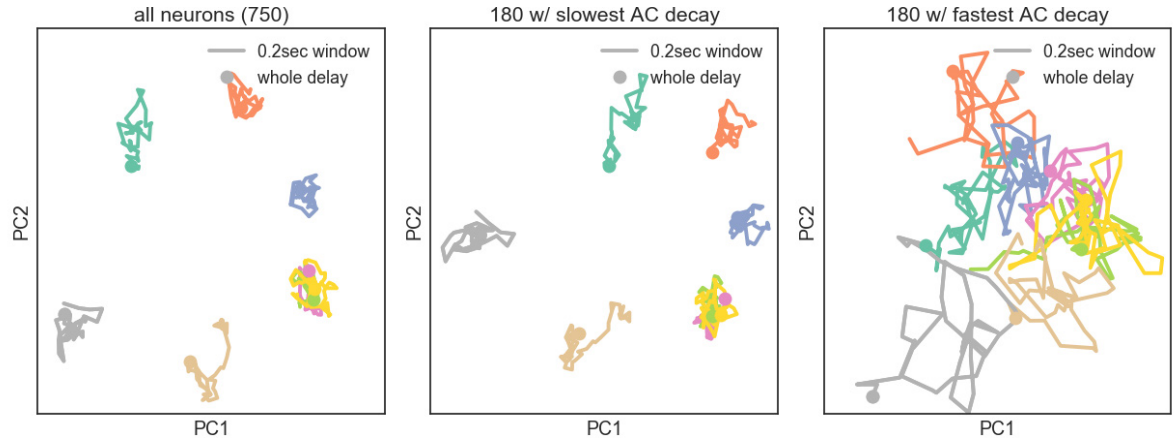

Disclosures: **K. Wimmer:** None. **J.M. Barbosa:** None. **A. Galán:** None. **C. Constantinidis:** None. **G. Mongillo:** None. **A. Compte:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: NSF Grant IGERT DGE-1069104

NIH Grant R01 MH112688

Title: Behavioral correlates of deliberation and habit on a contingency switching task for rats

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Abstract: Mammalian decision-making involves multiple separable systems, including deliberation (simulation of actions and evaluation of their outcomes) and procedural learning (recognition of a situation and the release of a well-learned action). Work in rodents on spatial mazes suggest that vicarious trial and error (VTE), a behavior where rats look back and forth at choice points in a maze, occurs in indecision during deliberation. Conversely, stereotyped paths through a maze appear to reflect procedural learning.
On many spatial tasks, animals deliberate early but transition to procedural behavior with experience. We designed a task which allowed animals to repeatedly transition from deliberative to procedural decision-making, but sporadically forced them back into deliberative mode. This task consisted of a topologically sideways figure-8 maze, with reward sites at the left and right sides and a third reward site at the base of the central track. The reward site at the center encouraged rats to stop and initiate new journeys from the same point. Reward was delivered under 3 contingencies: L (rats were rewarded at left and center for going left), R (rats were rewarded at right and center for going right), A (a different choice from the previous choice was required for reward). Rats were allowed to run freely on the maze for 60 min/session. The contingency changed randomly every 30+/-5 trials.
4 rats ran 185 +/- 37 trials per session, with at least 15 sessions per rat (one per day), and 5.5 +/- 1.4 contingency switches per session. VTE increased immediately after each contingency switch, and then decreased over the course of each contingency block, while path stereotypy decreased following each switch, and paths became more stereotyped over each contingency block.
To determine whether rats were aware of the contingencies, we fit a model-free reinforcement learning algorithm and a contingency-aware working memory algorithm to the behavior. The model-free algorithm explained rat choices better than chance; however, the contingency-aware algorithm explained rat choices significantly better than the model-free algorithm. VTE was correlated with uncertainty as to what contingency was in place.

Our results suggest that rats were aware of the contingencies, automated behavior within each block, and deliberated after contingency switch. Furthermore, VTE was related to indecision within the contingency-aware algorithm. The contingency switch task could be a promising avenue for investigating neural correlates of switching between deliberation and procedural decision-making.

Disclosures: B. Hasz: None. **A.D. Redish:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant T32 DA007234

NIH Grant R01 MH080318

NIH Grant T32 GM08471

Title: Indecisive behavior in response to environmental threat

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Abstract: Anticipation of future threat is a defining feature of anxiety. Many rodent models of anxiety use highly controlled environments that fail to replicate natural conditions where anxiety is typically experienced. Avoid-approach conflict tasks are thought to more closely mimic the internal and external conditions that result in the expression of anxiety in both health and disease by placing reward-seeking and threat-avoiding decision-making systems in conflict with one another. As a result, avoid-approach conflict tasks have emerged as a preferred paradigm for modeling human anxiety disorders.
A recent avoid-approach conflict task designed to amplify motivational conflict in an ecologically valid setting requires rodents to risk potential attack from a robotic predator each time they venture from an enclosed nest space to forage for food made available at the end of a linear track. This predator-inhabited arena task is run in four phases: Phase 1) linear track training, Phase 2) exposure to the robotic predator, Phase 3) the robotic predator attacks the foraging rodent, Phase 4) post-attack foraging.
Anxious behavior was quantified through three measures: mid-track aborts on outbound journeys (toward the predator), deliberative pausing at the exit of the enclosed nest space, and time spent occupying the nest zone. Mid-track aborts on return journeys (away from the predator) as well as

pausing and occupancy on other portions of the track provided controls. We tested six Brown-Norway (BN) rats (four males, two females) and four Fischer-Brown Norway first generation hybrids (FBNF-1) (two males, two females).
Brown Norway rats exhibited an increased number of anxiety-like hesitation behaviors (i.e. mid-track aborts, deliberative pausing, and nest-zone occupancy) during Phases 3-4 of the task. In contrast, FBNF-1 rats did not exhibit an increased number of hesitation behaviors across any of the four task phases.
These data corroborate a body of literature that identifies Brown Norway rats as being naturally more anxious than FBNF-1 rats. Furthermore, this work establishes new protocols for quantifying anxiety-like behaviors on the predator-inhabited arena, thus making several metrics available that can be used to measure anxious behavior using this task.

Disclosures: C.J. Walters: None. **A.D. Redish:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant F32 DA038392

NIH Grant R01 MH080318

Title: DREADD disruption of mPFC alters hippocampal economic decision making processes

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Abstract: While traversing an environment, hippocampal place cells fire in sequence within each theta cycle. These sequences have been hypothesized to reflect planning of future paths in both space and time. Previous work has found that the length of the theta cycle and the number of gamma cycles in any given theta cycle is related to the length of the spatial path represented by the sequence. Theoretical models have suggested that these planning processes entail interactions between hippocampus and medial prefrontal cortex (mPFC).
To test how mPFC affected hippocampal theta cycles and sequences, we reversibly disrupted mPFC with DREADDs while recording neural ensembles from the hippocampus and mPFC in rats trained on the spatial neuroeconomic task Restaurant Row. In this neuroeconomic task, rats run around a circular maze, encountering a serial set of skip or stay choices for differently flavored food reward. On each choice entry, rats hear a tone indicating the length of delay before

food will be delivered. Rats have 60min to gather their daily intake of food. Thus, rats must budget the delays that they will accept to maximize subjective value.
We measured theta (6-10 Hz) and gamma (25-55 Hz) oscillations during decision and control portions of the maze. Average theta period was longer in decision making epochs. Length of the theta cycle correlated with delay of the individual trial on the maze during the decision, suggesting that planning sequences depended on the length of the expected delay. Disrupting mPFC with CNO reduced hippocampal theta period and reduced this correlation, suggesting that disrupting mPFC disrupted theta planning processes. There were significantly more gamma cycles per theta cycle on the decision-making epoch compared to the control epoch. Disrupting mPFC with CNO reduced the average number of gamma cycles per theta cycle.
In decisions, rats will often pause and orient towards their optional trajectories, this vicarious trial and error (VTE) behavior is a reflection of deliberative decision making and indecision. We have previously reported that disrupting mPFC with CNO reduced VTE behavior. Theta period was larger for VTE than nonVTE entries, consistent with increased planning during VTE. Theta period was correlated with delay for both VTE and non VTE trials. However, only nonVTE trials showed this significant correlation on CNO days, VTE trials did not.
These data support the hypothesis that the length of a theta cycle is indicative of planning processes, and that mPFC engages with hippocampus during planning through a theta process, which was disrupted by our DREADD manipulations.

Disclosures: B. Schmidt: None. **A.D. Redish:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant F30 DA043326

MnDRIVE Neuromodulation Research Program

NIH Grant R01 MH080318

Title: Sunk costs and intertemporal choices in a neuroeconomic foraging task in mice

Authors: *B. SWEIS[1], A. E. MCLAUGHLIN[2], C. E. E. HUTCHINSON[2], D. M. MANCEBO[3], M. A. H. JONES[2], A. R. THOMPSON[2], M. THOMAS[4], A. D. REDISH[5]
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Abstract: Sunk costs are irrecoverable investments that can inflate the subjective value of a pursued reward. Intertemporal choice occurs when decisions have to be made between options with consequences occurring at different times, such as in foraging tasks. In foraging tasks, choices are often made between present and future rewards. If sunk costs inflate the subjective value of a reward, it may affect intertemporal choice, particularly present choices. Previous work has suggested that discounting rates can differ between intertemporal choices made between two future options and intertemporal choices which involve stay/leave options. It remains unclear whether mice are sensitive to sunk costs, and whether sunk costs interact with the perceived expenditure of time when making intertemporal decisions.
To test how sunk cost might differentially influence reward opportunity seeking decisions separate from reward taking decisions, we adapted a neuroeconomic foraging task for mice (Restaurant Row). In this task, mice were trained to forage for food rewards by running around a square maze with four distinct feeding sites (restaurants). As mice encountered each restaurant, the cost of waiting for food was indicated by pitch of a tone. Delays on each encounter were random from 1-30 sec. Each restaurant offered a unique flavor and contained separate offer and wait zones. Delay was indicated on entry into the offer zone, but did not start counting down until entry into the wait zone. If mice left the offer zone for the next restaurant (skip) or changed their minds after entering the wait zone (quit), the offer was rescinded and the tone ceased. Importantly, mice had a limited time on the track (60 min) to earn food for the day, so time had to be budgeted.
32 C57BL/6J male mice were trained for 65 days. Mice revealed stable economic preferences for different flavors similar to both rats and humans on these foraging tasks. Time spent within the offer zone deciding to accept or skip did not influence the likelihood of quitting in the wait zone despite detracting from the 60 min budget. However, time spent in the wait-zone decreased the likelihood of quitting compared to offers accepted with equivalent countdown time remaining yet with less prior time invested. These data suggest that mice are sensitive to sunk costs, but only in the wait-zone, in the patch itself. These findings suggest that the decision to choose between versus the decision to opt out may access different decision-making processes that are differently susceptible to sunk costs.

Disclosures: B. Sweis: None. **A.E. McLaughlin:** None. **C.E.E. Hutchinson:** None. **D.M. Mancebo:** None. **M.A.H. Jones:** None. **A.R. Thompson:** None. **M. Thomas:** None. **A.D. Redish:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 709.05/TT20

Topic: H.01. Animal Cognition and Behavior

Title: The role of extracellular matrix molecules for spatial representations in medial entorhinal cortex

Authors: *A. CHRISTENSEN[1], K. K. LENSJØ[2], M. E. LEPPEROD[3], M. FYHN[4], T. HAFTING-FYHN[1]
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Abstract: Perineuronal nets (PNNs) are specialized extracellular matrix structures that condense around the soma and proximal dendrites of mainly parvalbumin (PV+) expressing inhibitory neurons. During postnatal development, PNNs gradually mature and are thought to stabilize synaptic connections, restrict plasticity in the adult brain and perhaps play a role in remote memory storage. However, functional studies of PNNs for neural network- and cognitive function are lacking. Their role in spatial memory processing which likely depends on stable spatial representations in the medial entorhinal cortex (MEC), a hub in a distributed network of the brain's navigational system, has not been investigated. The spatially modulated 'grid cells'in the MEC possess a remarkable repetitive activity pattern. Grid cells are likely connected through a network of PV+ inhibitory neurons, suggesting that this network of inhibition is essential for the spatial representations of grid cells. Using a combination of local enzymatic degradation of the PNNs and single unit recordings in MEC of free-roaming adult Long Evans rats, we asked if the PNNs play a role in the grid cell network or spatial processing. Immunohistochemical mapping of the PNNs' expression patterns and cell type specificity in the MEC revealed that in addition to surrounding PV+ neurons, PNNs in MEC also co-localize with reelin and calbindin expressing neurons. Furthermore, we demonstrate that the maturation of PNNs in MEC coincides with the reported appearance of grid cell activity, while strong PV+ immunoreactivity is present from early postnatal age. In order to examine how PNNs contribute to spatial representations in the MEC, PNNs were enzymatically degraded and single unit activity was recorded using implanted tetrodes in MEC of rats exploring open fields (1x1m). To compare stored representations with the encoding of novel maps, the same units were recorded on consecutive trials in familiar and novel environments. Removal of the PNNs affects spatial representations and unit activity. Grid cells from MEC without PNNs in show show increased average firing rates and reduced spatial information. Simultaneously recorded putative inhibitory units show a trend of reduced average firing activity, which is in accordance with a recent report from visual cortex (Lensjo et al., 2017). When placed in a novel environment, gridness scores drop dramatically and grid cells show a lower spatial correlation throughout the recording session compared to grid cells from control animals. Together, these results indicate that PNNs may play a role for the stability of spatial representations of MEC in adult animals.

Disclosures: A. Christensen: None. **K.K. Lensjø:** None. **M.E. Lepperod:** None. **M. Fyhn:** None. **T. Hafting-Fyhn:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

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Program#/Poster#: 709.06/TT21

Topic: H.01. Animal Cognition and Behavior

Title: Perineuronal nets in the lateral secondary visual cortex are essential for remote visual fear memory

Authors: *E. H. THOMPSON[1], K. K. LENSJØ[1], M. B. WIGESTAND[1], T. HAFTING-FYHN[2], A. MALTHE-SØRENSSEN[3], M. FYHN[1]
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Abstract: Memories can last a lifetime even though the half-life of molecules found to be important for memory storage is much shorter. Preservation of connectivity of the involved network may therefore be facilitated by other and more stable molecular components, such as the extracellular matrix structure of perineuronal nets (PNNs). Here, we test this hypothesis in remote visual fear memories in adult rats. Recent evidence indicates that over time, visual fear memories become dependent on the lateral secondary visual cortex (V2L) (Sacco & Sacchetti, 2010). We asked if intact PNNs in V2L are required for remote visual fear memory. Remarkably, degrading PNNs using local injections of the enzyme Chondroitinates ABC (chABC) in V2L one week prior to remote memory retrieval selectively disrupted retrieval of the visual fear memory. The behavioral responses were supported by simultaneous recordings of local field potentials from V2L and basolateral amygdala (BLA) and revealed increased coherency between V2L and BLA in the theta range during memory recall in controls. However, in chABC treated animals no increased coherency was recorded, suggesting reduced or lack of synchronous activity between the brain regions at the time of the retrieval test. The effect was selective to the V2L as removal of the PNNs in the primary visual cortex had no effect on the fear memory. Furthermore, chABC injection in V2L before fear conditioning had no impact in acquisition or recent memory retrieval. Degrading PNNs after fear conditioning had no effect on recent memory, and remote memory could be retrieved properly if PNNs had time to regenerate before testing. These findings indicate that PNNs in V2L are critical for remote but not recent visual fear memory. Furthermore, based on our discoveries and the inherent properties of PNNs, we propose that PNNs are critical for stabilizing the neural network responsible for proper recall.

Disclosures: **E.H. Thompson:** None. **K.K. Lensjø:** None. **M.B. Wigestand:** None. **T. Hafting-Fyhn:** None. **A. Malthe-Sørenssen:** None. **M. Fyhn:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

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Program#/Poster#: 709.07/TT22

Topic: H.01. Animal Cognition and Behavior

Support: 231248

Title: Population density model of the entorhinal stellate-cell network with adaptation

Authors: *M. E. LEPPEROD[1], Y. LAI[3], M. FYHN[2], G. T. EINEVOLL[4], T. SOLSTAD[5], T. HAFTING[1], M. DE KAMPS[3]
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Abstract: The medial entorhinal cortex (MEC) is important for spatial memories and navigation and contains grid-cell networks. The grid-cells display a hexagonal spatial firing pattern with spiking coherent with theta (4-12 Hz) oscillations in the local field potential (LFP). One of the main cell types expressing the grid pattern with a strong inhibitory surround are the stellate cells, located in layer 2 of MEC. The biophysical properties of stellate cells are well-characterized but their interaction with the neural network in MEC remains elusive. While single cell sampling from vast networks of neurons yield important information about single cell function it fails to reveal population dynamics. In this study, we assessed the population response of MEC stellate cells to oscillating inputs in network simulations. Computations were performed with the MIIND simulator to describe the nonlinearity of adaptive dynamics underlying a noise process with high computational efficiency. The dynamics of the stellate cells were modeled as an adaptive phenomenon represented by a population-density model consisting of adaptive exponential integrate and fire (AdEx) neurons. The parameterized AdEx model reproduced temporal dynamics of stellate cells consistent with single cell patch-clamp experiments (e.g. resonance, sag, rebound spiking). In this parameter regime, the population density of the stellate cells was assessed over the model phase space. We show that this infinite population of stellate cells act as a bandpass filter resonating in the theta band, indicating that large-amplitude theta oscillations in MEC may be a network resonance evoked by disinhibitory inputs, likely from the medial septum. Furthermore, the adaptive dynamics of the AdEx neurons displayed strong transient responses when the population was primed with inhibitory input. The results of the present study show the limitations of predicting population dynamics of cell networks based on single cell experimental or modelling studies.

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Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

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Program#/Poster#: 709.08/TT23

Topic: H.01. Animal Cognition and Behavior

Title: Conditional knock-out of the ACAN gene removes aggrecan and perineuronal nets in adult mice and induces life-long brain plasticity

Authors: *K. K. LENSJØ[1], D. ROWLANDS[3], T. DINH[2], M. R. ANDREWS[4], T. HAFTING-FYHN[2], M. FYHN[2], J. W. FAWCETT[3], G. DICK[2]
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Abstract: Perineuronal nets (PNNs) are a specialized form of extracellular matrix in the CNS that mainly enwraps parvalbumin (PV) expressing inhibitory interneurons. They assemble in parallel with the maturation of the inhibitory network and with the closure of critical period plasticity. Several lines of evidence support a role for PNNs in stabilizing synapses and limiting adult brain plasticity. While the mature PNN is a complex structure of several components, recent work suggests that the proteoglycan aggrecan, a product of the ACAN gene, is essential for the PNNs. However, because aggrecan is also an integral part of cartilage throughout the body, global ACAN knock-out is lethal. Thus, to investigate the role of aggrecan for PNN assembly and stability, and its contribution to brain plasticity, we established a CRE-inducible conditional ACAN knock-out mouse. The transgenic construct is a design of the European Conditional Mouse Mutagenesis Program and has had two loxP sites inserted into the genome, flanking exon 4 of the ACAN gene. Two approaches were used to remove aggrecan from these mice, either by (1) injecting a viral vector expressing CRE recombinase under control of the synapsin promoter to obtain area specific knock-outs in adult mice, or (2) crossing with Nestin-Cre mice for global neuron knock-out. Aggrecan and PNNs were determined by immunohistochemical staining against aggrecan, the PNN specific lectin *Wisteria floribunda* agglutinin and other components of the PNN. In the visual cortex, local injections of AAV9.Syn.Cre caused removal of WFA and aggrecan staining. Activity-dependent plasticity was induced by monocular deprivation and assessed by intrinsic optical signal imaging. Removal of aggrecan caused persistent ocular dominance plasticity in adult mice. Furthermore, the ACAN-Nestin-Cre mice lacking PNNs in the entire brain showed enhanced performance in a spontaneous object recognition task. Taken together, our results provide the first direct evidence that aggrecan is the main functional constituent of PNNs restricting plasticity. Our studies promote the ACAN mouse as a robust tool to investigate the role of PNNs in plasticity and disease

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Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 709.09/TT24

Topic: H.01. Animal Cognition and Behavior

Support: SPP 1392

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BCCN Munich and Synergy Cluster of Excellence Munich

Title: Sensory-motor coordination during spontaneous exploration of rats

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Abstract: Active sampling of the environment entails a coordination of sensing and action. One of the major components of the sensory experience of a rodent exploring their environment is the sense of smell. The odor space is sampled rhythmically, driving air in and out of the nose at frequencies ranging from 6 to 12 Hz. This sniffing behavior is not only related to odor sampling but also modulated, by expectation and motivation. Detailed experiments have shown the sniffing cycles constitutes the unit of sensory processing during both detection and discrimination, coordinating the neural processing of the odor information. Nevertheless, how sniffing behavior is coordinated with other sensory modalities and integrated within the rich behavior expressed by freely-moving rodents when exploring their surroundings has been less studied. To gain an understanding of a more naturalistic organization of exploration in rodents and its relationship with sniffing behavior, we recorded pressure sensor signals from the nasal cavity of rats concurrent with high-resolution body tracking during spontaneous exploration. We identified discrete behavioral modes: walk, rear, turn, pause, groom, and sit, each behavior showing a characteristic correlation of kinematic and postural variables, allowing generalized classification between individuals. Rats explore their surroundings in “bouts” of activity composed of several of the behaviors described. During these “bouts” we observe the coordination between sniffing and head movements constrained within 6 to 12Hz. Head motion shows a stereotypic displacement in the 3d space, with excursions defined by the peaks of inhalation and exhalation. Detailed analysis of the direction of motion between peaks of inhalation and exhalation shows than this coordination is mostly expressed at lower head pitch when the tip of the nose is near the floor, reflecting potentially, the synchronization with

whisking, in sharp contrast, when the nose is far from the ground this coordination is less frequent and change in phase. Furthermore, this sensory-motor coordination is occurring simultaneously with different behaviors of rats and changes within the trial. Overall our results show that the sensory-motor coordination occurring during spontaneous exploration changes dynamically, depending potentially, on the demands for coordinated processing of different streams of sensory information.

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Poster

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German Research Association (DFG) via RTG 2175

Title: Capturing attractor dynamics in hippocampal place cell remapping through micro-endoscopic imaging in freely moving mice

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Abstract: The hippocampal formation plays a fundamental role in the acquisition, consolidation and retrieval of episodic memory as well as in spatial navigation. A potential key mechanism supporting stable yet flexible representations of space within the entorhino-hippocampal formation are attractor dynamics. Attractor networks have been used to describe various brain functions, such as memory, classification, and motor behavior and have long been proposed to underlie stable place, grid and head direction components of spatial representation. Attractor properties of hippocampal spatial maps have been linked to the phenomenon of abrupt remapping of place fields elicited by morphing of environmental cues. The study of hippocampal attractor dynamics, which are thought to operate at the population level, has until now been limited by the relative difficulty of recording sufficiently large populations of cells across days. The recent development of head-mounted microscopes enabling imaging activity of large

neuronal ensembles over long periods of time in freely moving animals gives us now the opportunity to go into a deeper characterization of attractor dynamics. We have used micro-endoscopes (UCLA Miniscope) to record large ensembles of neurons in hippocampal area CA1 while manipulating the external environment. We habituated male mice to two connected environments that differed in visual, tactile and auditory features, both containing an empty compartment. To probe the basin of attraction of the hippocampal representations of these two environments we briefly exposed the animal to an environment with intermediate features compared to the two previous ones. Next we introduced a female into the compartment of one of these original environments, which resulted in an increased preference of the male mouse for this environment in subsequent retrieval sessions without female. We compared levels of remapping between all three environments, testing if the valence of a female-paired environment leads to differential expression of the basins of attraction of hippocampal CA1 spatial maps. In the next set of experiments we are investigating attractor properties of hippocampal representation via controlled manipulation of the visual environmental features using a virtual environment for freely moving animals. We expect that these experiments will contribute to better understanding of attractor dynamics associated with hippocampal remapping phenomenon.

Disclosures: E. Itzcovich: None. **N. Karalis:** None. **A.V. Herz:** None. **A.M. Sirota:** None.

Poster

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Support: Munich Cluster for Systems Neurology (SyNergy, EXC 1010, Munich)

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Title: Slow oscillations in the lateral and medial entorhinal cortex differentially couple to hippocampal ripples in non-anaesthetized sleeping rats

Authors: *G. SCHWESIG, J. MARTINEZ ALCANTARA, A. SIROTA
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Abstract: Synchronous activity associated with hippocampal sharp-wave ripple events occurring during offline brain states has been implicated in systems memory consolidation, associated with a shift of memory trace retrieval dominance from hippocampus to neocortex. During sleep this process is thought to rely on the temporal coordination of neural activity in both hippocampal and cortical circuits emerging from the biasing of hippocampal sharp-wave ripple occurrence by

the down-up transitions of neocortical slow oscillations. However, the distributed and heterogeneous nature of neocortical slow oscillations calls for a refinement of this early model. Importantly, the lateral and medial entorhinal cortices are the major cortical gateways of the hippocampal formation, connecting it bidirectionally with widespread but distinct neocortical networks. To examine if cortical slow oscillations and hippocampal ripple dynamics during sleep are differentially coupled via these distinct gateways, we recorded unit activity and local field potentials across layers of the dorsal hippocampus (HPC), lateral (LEC) and medial entorhinal cortex (MEC) in freely moving and sleeping rats. Analysis of the up-down state transitions in MEC and LEC shows that slow oscillations dynamics in the two structures are qualitatively distinct and only weakly temporally correlated. Moreover, HPC sharp-wave ripples were differentially entrained by LEC and MEC slow oscillation dynamics. To further elucidate this effect we investigate the bidirectional effect of HPC ripples and LEC/MEC Up states on respective target structures via anatomically-resolved current-source-density signal analysis. These results imply that the interaction of cortical slow oscillations and hippocampal ripples is not globally synchronous and is differentially gated via two entorhinal circuits, providing a possible framework for distinct brain-wide memory consolidation sub-systems.

Disclosures: **G. Schwesig:** None. **J. Martinez Alcantara:** None. **A. Sirota:** None.

Poster

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Title: Respiratory entrainment of memory circuits

Authors: *N. KARALIS, A. SIROTA
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Abstract: Decades of research have identified neural oscillations as a mechanistic substrate for the formation of cell assemblies and the coordination of information transfer between remote brain regions. During exploratory behavior, the hippocampus and the prefrontal cortex are organized by theta oscillations, known to support memory encoding and retrieval, while during sleep the same structures are dominated by slow oscillations that are believed to underlie the consolidation of recent experiences.

Although most known neural oscillations are generated by intra-cerebral pacemakers and circuits, here we focused our attention to breathing, the most fundamental and ubiquitous rhythmic activity in life. We report respiratory entrainment of limbic circuits, including the prefrontal cortex and hippocampus, two structures critically involved in memory consolidation and retrieval.
Using a combination of extracellular recordings using high-density silicone probes, calcium imaging, photometry, pharmacological and optogenetic manipulations in mice, we identify that a rhythmic oscillation (2-6 Hz and termed respiratory θ rhythm) entrains neuronal activity across structures. We characterize the translaminar and transregional profile of the respiratory entrainment of the prefrontal cortex and hippocampus and demonstrate a causal role of re-afferent respiratory inputs in synchronizing neuronal activity and network dynamics between these structures in a variety of behavioral scenarios in the awake and sleep state. Prefrontal 4Hz oscillations, recently identified as a physiological signature of fear memory in mice, are a manifestation of the differential cortical entrainment by the respiratory θ rhythm during behavior. Our results highlight respiration, a persistent rhythmic input to the brain, as a novel oscillatory mechanism mediating inter-regional synchronization of limbic memory circuits and contributing to the formation and expression of neuronal ensembles.

Disclosures: **N. Karalis:** None. **A. Sirota:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

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Title: Impaired spatial reorientation in the 3xTg-AD mouse model of Alzheimer's disease

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Abstract: Spatial navigation is affected early in the symptopathology of Alzheimer's disease (AD), since deterioration of spatial navigation is observed in prodromal cases of this disease. A preponderance of evidence suggests that the internal map of the environment is represented in

world-centered (allocentric) coordinates; however, movements and perception of the environment are in body-centered (egocentric) coordinates. Therefore, in order to navigate, it is essential for coordination and translation between these coordinates. Parietal cortex (PC) and hippocampal activity patterns play a key role for transforming landmark representations from egocentric to allocentric coordinates. Emerging findings suggest abnormal communication between the PC and hippocampus in preclinical AD cases may be involved in impaired navigation in AD. Here, we seek to investigate in a preclinical model of AD, the 3xTg-AD mouse, the molecular mechanisms by which spatial orientation is impaired in AD.
We assessed 3xTg-AD mice in male (6 & 13 months) and female (3 & 6 months) mice using a task previously shown to be sensitive to impaired hippocampal map realignment. This task requires mice to learn and remember the spatial location of a small reward zone that is in a fixed location with respect to distal cues, but otherwise unmarked. Mice were trained to shuttle to the end of a track and back to an enclosed start box to receive a water reward. Next, bilateral stimulating electrodes targeting the medial forebrain bundle were implanted, and mice were trained to continue shuttling for water, but also stop in the reward zone to receive a brain stimulation reward. The track slides to a random start location for each trial. Thus, distal but not local cues were informative. The time required to remain in the zone for a reward was increased in 0.5s increments from 0.5-2.5s across training.
We found that female 3xTg-AD mice showed a more pronounced impairment than male 3xTg-AD mice compared to non-Tg age/sex-matched controls. Specifically, by 6 months female mice had robust impairments in the proportion of correct trials. In addition, 6-month female 3xTg-AD mice slowed significantly less slowing than controls in the reward zone. The impairments observed in 3xTg-AD mice are not explained by differences in reward responding, as operant responding for reward did not differ in 3xTg-AD mice compared to non-Tg controls. Thus, AD may cause spatial disorientation as a result of impaired use of landmarks to maintain spatial orientation. We are recording from the PC and hippocampus in 6-month female 3xTg-AD mice to assess a potential role of the PC-hippocampal network in AD-related impaired spatial reorientation.

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Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

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Title: Decoding kinematic motion from neural recordings in the parietal cortex using a generalized linear model

Authors: I. SKELIN[1], W. WU[2], B. L. MCNAUGHTON[3], *A. A. WILBER[2]
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Abstract: The parietal cortex (PC) neuronal populations show tuning to self-motion state, a compound measure of linear and head angular velocity. Self-motion tuning in PC is organized at the modular level, where the tuning parameters are similar across the cortical layers, but have sharp boundaries in the lateral directions. This study develops a Bayesian state-space framework to decode the self-motion state from pooled multineuronal activity or high frequency local field potential (HF-LFP) envelope simultaneously recorded from up to 18 tetrodes in rat parietal cortex in rats that had been trained to either run a cued random spatial sequence to 32 light locations evenly spaced around the perimeter of a circular platform. We encoded the neural data using a generalized linear model, which assumes that the multineuronal activity or HF-LFP envelope amplitudes on a single tetrode follow a Poisson distribution whose mean depends on a normalized combination of linear and head angular velocity. This model is learned from training data along with a linear Gaussian model that characterizes kinematic motion over time. Inference of kinematics is performed using a point process filter which gives an efficient recursive method in real-time. Two-fold cross-validation was performed on four datasets from two rats and has shown a high decoding accuracy, with averaged correlation coefficient being 0.60 (±0.05) for multineuronal activity and 0.67 (±0.03) for HF-LFP-based model. The present results demonstrate the high predictive validity of the population activity in PC for decoding the self-motion state.

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Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

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NSERC

Title: Hippocampus is necessary for intact retrosplenial place cell activity

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Abstract: Hippocampal place cell ensemble shows sequential activation that is locked to position when animals move in an environment. Computational models hypothesize that the hippocampus generates an indexing code that is broadcasted to the entire neocortex to associate information across different modalities. The format of this indexing code, and the neocortical regions that mediate this information flow is unknown. The retrosplenial cortex (RSC) is immediately connected with the hippocampal formation. Neurons in RSC exhibit similar activation patterns to hippocampal place cells during the same task. Whether the hippocampus contributes to the generation of retrosplenial place cell activity or vice versa is unclear. To address this question, we combined hippocampus lesion (NMDA excitotoxic lesion; 2 lesion sites, AP: -2.3, ML: 1.5, DV: 1.8 and AP: -3.2, ML: 2.5, DV: 2.0) with 2-photon calcium imaging of superficial RSC neurons in head-fixed mice (Thy1-GCaMP6s GP4.3 transgenic mice) during a virtual path integration task. RSC place cell fraction was similar between mirrored left and right hemispheres ($p = 0.20$, paired t-test; $n = 5$ mice). Bilateral, but not unilateral, dorsal hippocampus lesion significantly disrupted RSC place cell fraction ($p < 0.05$, one-way ANOVA; $n = 3$ mice with intact hippocampus, $n = 3$ mice with unilateral hippocampus lesion, $n = 4$ mice with bilateral hippocampus lesion) and reduced position decoding accuracy ($p < 0.05$, one-way ANOVA) when taking the entire imaged neuron population into consideration. These results indicate that the hippocampus is necessary for the expression of intact place cell activity in RSC.

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Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

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Title: Hippocampal contributions to V1-dependent memory and plasticity

Authors: *P. S. FINNIE[1], Y. LI[2], H. KIM[2], S. F. COOKE[3], M. F. BEAR[1]
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Abstract: The requirement for hippocampus is well established for several forms of memory, yet the specific encoding functions this structure supports remain poorly understood. Several theories posit that hippocampus rapidly encodes ongoing multimodal sensory experience, which is then processed by more stable neocortical circuits to gradually extract underlying statistical regularities. Yet accumulating evidence is beginning to reveal the capacity for rapid neocortical plasticity, even following brief hippocampus-dependent episodes. If the requirement for hippocampus during a given task is not a consequence of the slow rate of neocortical plasticity, then what does this structure contribute to memory encoding? The hippocampus is a major component of the limbic system, which controls neuromodulatory signaling throughout the brain. Such modulation robustly drives protein synthesis, which is typically necessary for long-term memory consolidation. Thus we hypothesized that even forms of long-term memory and plasticity reliant primarily on primary visual cortex (V1) should be subtly disrupted by hippocampal ablation. To test this possibility we used a simple visual training protocol in which an oriented grating stimulus is repeatedly presented to mice over days. This training produces both behavioral (orientation-selective habituation; OSH) and electrophysiological (stimulus-selective response potentiation; SRP) changes that can each be assessed at short-term, long-term, and remote time-points. We report that mice receiving either excitotoxic or sham lesions of hippocampus exhibit no significant differences in either measure. The percent change in electrophysiological evoked responses may even be enhanced in mice lacking hippocampus, although this dissipates prior to remote testing sessions. Lesions were confirmed both behaviorally and histologically. We also observed little impact of transgenic NMDA-receptor knockout restricted to hippocampus. We conclude that hippocampus is not required for the acquisition or expression of this form of visual recognition memory, but may influence systems-level consolidation processes in neocortex.

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Poster

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Title: Communication between the hippocampus and olfactory system is needed for contextually cued retrieval of odor memories

Authors: *N. HERNANDEZ[1,2], L. RAIT[2], J. DOBBIN[3], T. CLELAND[2], C. LINSTER[3], D. M. SMITH[2]
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Abstract: Context is a potent retrieval cue. Many studies have shown that unique ensembles of hippocampal neurons are activated in each environment a subject encounters. Upon revisiting a familiar environment, these hippocampal context representations are automatically reactivated and they prime context-appropriate behaviors and memories. Individual sensory cues are thought to be represented in primary sensory areas and those representations are also reactivated during retrieval. Thus, communication between the hippocampus and primary sensory areas may underlie contextual priming of memory. Olfaction provides an excellent way to study memory in rodents and there is a direct pathway from the ventral hippocampus (vHPC) to the anterior olfactory nucleus (AON), a structure known to modulate processing in the olfactory bulb and piriform cortex. Thus, this pathway could mediate top-down context-based modulation of olfactory memory by the hippocampus. To test this hypothesis, we trained rats on a contextually cued odor discrimination task. Rats learned to dig for a reward in one cup of odorized digging medium (odor A) and to refrain from digging in a different cup (odor B) when they were presented in one context (the black side of the box). The reward contingencies were reversed when the same odor cues were presented in the other context (the white side of the box). Thus, the rats had to use the context (black or white) in order to guide their choice behavior. After rats learned the task, we conducted three temporary inactivation experiments. In the first two experiments, we performed bilateral inactivation of the AON and vHPC. In the third, we used cross-hemisphere infusions of muscimol (i.e. inactivation of the vHPC in one hemisphere and the AON in the other) in order to disrupt vHPC-AON communication. All three inactivation procedures significantly impaired performance (vHPC: $t(5)= -7.72$, $p < 0.001$ and AON: $t(5)= -6.52$, $p < 0.001$, compared to saline controls; cross-hemisphere inactivation: $F[2,4]= 46.619$, $p < 0.001$, compared to saline and unilateral muscimol controls). These results indicate that each structure is independently needed and moreover, that communication between the vHPC and AON is critical for contextually cued odor memory. This supports the general hypothesis that contextual priming of memories involves hippocampal modulation of primary sensory representations.

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Poster

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Title: Rapid sensory-evoked modulation of hippocampal spatial activity

Authors: *R. ZEMLA, M. DUFOUR, S. SUNDAR, A. HAIRSTON, J. BASU
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Abstract: Rapid association of relevant sensory events in the environment with their spatial location is important for the formation and recall of episodic memories. The dorsal CA1 region of the hippocampus exhibits spatially-selective activity in its excitatory pyramidal neurons. As an animal navigates through its environment, place cells fire at distinct spatial locations - also known as place fields - which stabilize with experience. Long-range projections from layers II and III of the medial entorhinal cortex (MEC) convey spatial information to the dendritic tree of CA1 pyramidal neurons via direct and indirect pathways. Interestingly, the neighboring lateral entorhinal cortex (LEC), which integrates polymodal sensory, novelty- and context- related information also sends projections to CA1 pyramidal neurons. While there is a gradient in the anatomical distribution of the MEC and LEC inputs along the proximal-distal axis of area CA1, pyramidal neurons in the medial CA1 sub-region receive inputs from both MEC and LEC. Additionally, MEC and LEC inputs are conveyed trisynaptically from dentate gyrus and CA3 through the Schaffer collateral pathway to integrate sensory and spatial information contents routed from LEC and MEC. The convergence of spatial and sensory information onto the same population of neurons in CA1 suggests that changing environmental sensory input may modulate spatially-dependent CA1 activity. Using in vivo two-photon imaging, we tested this hypothesis by first establishing that CA1 pyramidal neurons and interneurons show somatic calcium activity in response to odor stimulation *in vivo.* Using mice trained to navigate head-fixed on a textured treadmill track , we are now testing how enrichment of specific spatial zones on the track with odor stimuli influences the spatially tuned calcium activity of CA1 pyramidal neurons. Furthermore, by performing volumetric imaging of somatic and dendritic planes of CA1 pyramidal neurons we are assessing how manipulation of genetically defined local and long-range inhibitory inputs shape short-term and long-term changes in sub-compartment specific calcium activity during an odor-place association task.

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Poster

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JTT/MUM/INST/IIOS/2013-14/0033

Title: Retrieval specificity of remote memory is affected by the order of retrieval

Authors: *A. SINGH, S. KUNDU, R. SUGANDHITA, S. KUMAR, A. DAS, J. BALAJI
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Abstract: Retrieval of memories long time after their acquisition has been shown to depend on training conditions. In order to consider the nature of remote memories, the role of cortico-hippocampal connections has been debated for a long time across theories such as standard model and multiple trace theory. While various training conditions have been considered to understand memory retrieval, testing conditions have been looked at in a relatively uniform manner across existing studies. One aspect that has received minimal attention is that during testing, each retrieval event is also a new learning experience. We propose that the learning experience during remote memory retrieval modulates the memory trace in a different manner in comparison to recent memory retrieval. In our study, such effect is evident as the specificity of remote memory is found to be affected by the order of testing.We explore this phenomenon with novel modifications in rodent behavior protocols for generalization and discrimination testing of contextual fear memory. First, we propose a theoretical description for a model of remote memory retrieval emerging from our study in order to incorporate the effect of new learning during retrieval. We then test the effect of retrieval order on remote memory specificity with mice and show that specific testing conditions can allow recall of such hard-to-find memories. Using hippocampal lesions, we find hippocampus to be required for manifesting the effect of retrieval order on the specificity of remote memory. Further, we explore the neuronal underpinnings of this phenomenon using in vitro and in vivo imaging techniques coupled with our behavior paradigms.

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Department of Biotechnology, Ministry of Science and Technology: DBTO/BCN/BJ/0402

Tata Trusts: JTT/MUM/INST/IIOS/201314/0033

Council of Scientific and Industrial Research: 09/079(2697)/2016-EMR-I

Title: An *In vivo* approach to identify and segregate neuronal ensembles of multiple memories using temporal expression dynamics of a single immediate early gene

Authors: *M. PRABOD KUMAR[1], S. KUMAR[2], T. CHERIAN[2], B. JAYAPRAKASH[2]
[2]Ctr. for Neurosci., [1]Indian Inst. of Sci., Bengaluru, India

Abstract: Immediate early genes (IEGs) are widely used as a marker for neuronal plasticity. Yet, techniques to identify the temporal coupling of IEG expression to different behaviors or events (e.g. cellular compartment analysis of temporal activity by fluorescent in situ hybridization (catFISH), Fos-tTA,Tet-tag transgenic mice) are limited. All these techniques are limited to *in vitro* applications and provide a snapshot of the different neuronal populations that were activated during behavior. However, if one were to follow these populations *in vivo* then it amounts to several imaging sessions that are interspersed between behavioral tasks. This leads to anesthetizing the mice several times for identifying these neurons. Further, if one were to investigate the synchronous IEG activation of the neurons in an ensemble, it is harder and in many instances it is not viable. Here, we model the dynamics of an IEG expression *in vivo* and experimentally show that this approach can be used to identify distinct neuronal subsets. The rationale is to use the kinetics of expression to estimate when the activity of the neuron was induced. We present a generalized theoretical framework of such a dynamical system. We show that the fluorescence measurement of cFOS-EGFP protein in the transgenic mice over time, from

the onset of stimulus, is well fit to an analytical expression derived to describe the above model. Using this approach we obtain the general method by which we are able to distinguish between neurons that took part in multiple events that are separated in time, by looking at the level of fluorescence of individual neurons.

Disclosures: M. Prabod Kumar: None. **S. Kumar:** None. **T. Cherian:** None. **B. Jayaprakash:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

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Tata Trust grant JTT/MUM/INST/IIOS/201314/0033

Title: Systems consolidation of temporal content in episodic memory

Authors: *S. SHRIDHAR, V. PAL SINGH, S. KUNDU, B. JAYAPRAKASH
Ctr. for Neurosci., Indian Inst. of Science, Bengaluru, Bengaluru, India

Abstract: Episodic memory is remembering the what, when and where of an autobiographical event. In this regard, the concept of time in autobiographical memory is fundamental to human experience. In animal models, it has been shown to have important implications in foraging behavior. We know that memories once acquired change over time; they might lose the richness of detail and generalize the stimulus they were presented with and their contextual information. However, very little is known about the nature of temporal aspects of these memories and to what extent they are preserved over time. Our current research aims to understand consolidation of temporal memory, and how it evolves over time.
We have modified behavioral paradigms and have designed novel flavor place association tasks that introduce an explicit temporal component, Through these paradigms the mice are trained and

are tested for different aspects of temporal memory during retrieval to study how these aspects evolve during the process of systems consolidation.

Disclosures: S. Shridhar: None. **V. Pal Singh:** None. **S. Kundu:** None. **B. Jayaprakash:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 709.22/TT37

Topic: H.01. Animal Cognition and Behavior

Support: MCIT

Title: Single galvo based simultaneous glu-uncaging and imaging using single ultrafast laser system

Authors: *S. SAUMITRA[1], V. R. SINGH[1], S. K. SIKDAR[2], A. GHOSH[1], J. BALAJI[3]
[1]Ctr. For Nanoscience and Engin., [2]Mol. Biophysics Unit, [3]Ctr. For Neurosci., Indian Inst. of Sci., Bangalore, India

Abstract: Two-photon uncaging combined with calcium imaging is a critical experimental tool to investigate synaptic plasticity rules in a spatio-temporal scheme. In order to perform simultaneous uncaging and imaging, typically ultrafast laser pulses from two separate laser systems are used in conjunction with two independent sets of galvanometric mirrors. However, such a setup is instrument intensive and requires synchronized operation of two laser systems making it relatively tedious to operate and maintain. Here, we report a single ultrafast laser system based optical setup that uses a single set of galvanometric mirror based regular scanning assembly to perform simultaneous two-photon uncaging and calcium imaging in a hippocampal neuron. A fast operating optical shutter operating along with our delay line optics and galvanometric mirror is used to generate patterned uncaging excitation. Spatial control of uncaging is measured and shown to be close to the optical resolution. The accuracy and synchrony is shown to be within few microseconds. We put to use the good control of uncaging location in these experiments to investigate the cooperative and associative plasticity.

Disclosures: S. Saumitra: A. Employment/Salary (full or part-time):; PhD Student, Indian Institute of Science. **V.R. Singh:** None. **S.K. Sikdar:** None. **A. Ghosh:** None. **J. Balaji:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 709.23/TT38

Topic: H.01. Animal Cognition and Behavior

Support: Council of Scientific and Industrial Research:-09/079(2561)2012-EMR-I (CSIR Fellowship to Suraj K.)

Department of Biotechnology,Ministry of Science and Technology:-DBTO/BCN/BJ/0402

Department of Science and Technology,Ministry of Science and technology:-DSTO/BCN/BJ/1102

Department of Science and Technology,Ministry of Science and technology:-DSTO/BCN/BJ/1297

Tata Trust:JTT/MUM/INST/IIOS/201314/0033

Title: Fluorescence saturation dynamics based *In vivo* classification of spines

Authors: *S. KUMAR[1], B. JAYAPRAKASH[2]
[1]Ctr. for Neurosci., Indian Inst. of Sci., Bangalore, India; [2]neurobiology, Indian Inst. of Sci. Malleshwaram Bangalore, Bangalore, India

Abstract: In this work we present a new method that utilizes optical saturation to measure absolute absorption cross section. Until recently it has not been possible to measure absorption cross-section in absolute manner *under a microscope*. Here we propose a method that utilizes parameters that characterizes optical saturation to estimate absolute cross-sections of fluorophores independent of concentration, collection efficiency and other such parameters that is difficult to account for. Our method is easily implementable in any confocal/multi-photon microscope to image the cross-section as a function of space across the sample. This made it possible for us to propose a new imaging contrast (β) representing the local micro-environment of the fluorophores. We have used this method for *in vivo* imaging of mice to generate information based on the parameter (β) that allows for classification of spines. The spines imaged in a field of view can be classified using the relative contrast parameter. Imaging the spines longitudinally and with behavioral manipulations reveal the functional significance of imaging contrast (β) in spines. In addition, we demonstrate the generality of our method by measuring the absolute three photon cross-section of L-tryptophan (reported for the first time).

Disclosures: S. Kumar: None. **B. Jayaprakash:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 709.24/TT39

Topic: H.01. Animal Cognition and Behavior

Support: DBTO/BCN/BJ/0402

DSTO/BCN/BJ/1102

DSTO/BCN/BJ/1297

JTT/MUM/INST/IIOS/201314/ 0033

Title: Bayesian nature of remote memory assisted learning (mental Schema) and its role in problem solving in mice

Authors: *V. SINGH[1], R. BHATT[1], S. KUNDU[1], S. SHRIDHAR[1], S. SAUMITRA[2], A. SINGH[1], B. JAYAPRAKASH[1]
[1]Ctr. for Neurosci., [2]Ctr. for Nanoscience and engineering, Indian Inst. of Sci., Bangalore, India

Abstract: Memories of related events and facts are thought to be stored in neocortex in the form of associative networks (mental Schema). The dynamics for consolidation and retrieval are different from that of single event learning. Although neocortex is shown to be involved, but no mathematical/statistical model has been proposed and tested to explain the evolution of a mental schema and how it can assist learning of similar information rapidly. In order to address this we trained animals to learn same sets of flavour place associations (paired associates) in two different ways viz., i) Solitary Learning: Two sets of association are presented independently one after the other ii) Relational Learning: Second set is presented in relation to first set. We find that only the animals that underwent relational learning were able to acquire both set of flavours. We show that older memories help in acquisition of new memories only if presented in a relational manner. We hypothesise and show that such behaviour is consequence of Bayesian learning mechanisms of the neocortex.

Disclosures: V. Singh: None. **R. Bhatt:** None. **S. Kundu:** None. **S. Shridhar:** None. **S. Saumitra:** None. **A. Singh:** None. **B. Jayaprakash:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 709.25/TT40

Topic: H.01. Animal Cognition and Behavior

Support: Kaken-hi (15H05569)

Kaken-hi(15H01417)

Title: Acute effects of social defeat stress on cortical neuronal activity

Authors: *R. NAKAYAMA, T. SASAKI, Y. IKEGAYA
Grad. Sch. of Pharmaceut. Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: Stressful experiences cause a variety of dysfunctions in the body. As early studies have focused on biological phenomena restricted within a single peripheral organ, it remains to be elucidated how the organ activity is affected by the brain and autonomic nervous system during stress responses. To address this question, electrophysiological changes in cortical and cardiac activity were recorded from rats that were subject to social defeat stress. In stress-susceptible rats, which showed a significant decrease in heartbeat rates after the stress load, the power of cortical local field potentials was attenuated immediately and transiently in response to social stress. These power decreases occurred across multiple brain regions, including the hippocampus, the neocortex, and the thalamus. In addition, cerebral microdialysis revealed that the extracellular concentration of serotonin, a monoamine neurotransmitter, was pronouncedly increased after social stress. These dynamic changes in cortical activity may be a possible mechanism to disrupt peripheral organ functions in response to mental stress episodes.

Disclosures: R. Nakayama: None. **T. Sasaki:** None. **Y. Ikegaya:** None.

Poster

709. Learning and Memory: Cortical-Hippocampal Interactions

Location: Halls A-C

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Program#/Poster#: 709.26/TT41

Topic: H.01. Animal Cognition and Behavior

Support: SURE Grant

Funding from USD College of Arts & Sciences

Title: Interaction of multiple memory systems during spatial alternation task in the rat

Authors: *N. T. REITZ, J. L. VINCZE, J. B. HALES
PSYCHOLOGICAL SCIENCES, UNIVERSITY OF SAN DIEGO, SAN DIEGO, CA

Abstract: Multiple memory systems in the brain work to successfully form declarative and non-declarative long-term memories. Declarative memories, memories for facts and events, are encoded by the medial temporal lobes, including the hippocampus, whereas non-declarative memories are formed in other regions of the brain, including the neocortex, striatum, and amygdala (Squire, 2004). Although the hippocampus is critical for declarative memory formation, hippocampal-lesioned rats are often still able to reach control levels of performance over time on typically hippocampus-dependent tasks (Morris & Frey, 1997; Hales et al., 2014), suggesting the recruitment or ongoing involvement of an alternative memory system. Our study is designed to probe two possibilities of memory system interaction. One possibility is that an alternative memory system, such as the striatal system, compensates for the damaged hippocampus and only engages if the hippocampus is not functional. Another possibility is that the striatal memory system is always engaged in gradually learning the spatial memory task, but the more efficient and dynamic hippocampal memory system masks, or even inhibits, any contribution from the striatum (Sutherland et al., 2010). To examine these possibilities, we tested rats with bilateral excitotoxic hippocampal lesions or sham lesions on the alternating T-maze task. Once rats consistently alternate, a 10-second delay was added between trials, as previous studies have shown that a 10-second delay will disrupt performance in hippocampal-lesioned rats (Ainge et al., 2007). All rats were trained until they reached criterion performance. For the hippocampal-lesioned rats and half of the sham rats, 90 minutes after the last training session, the rats were perfused and brains were stained for c-Fos expression using immunohistochemistry. The other half of the sham rats continued training past criterion until the number of testing days matched the number for each hippocampal-lesioned rat, using a yoked design. These "overtrained" sham rats were then perfused, and brains were stained for c-Fos. The critical comparisons for the overtrained sham rats is the level of c-Fos expression in the hippocampus compared to the other sham rats and in the striatum compared to the hippocampal-lesioned rats. Such comparisons directly examine the relative contributions of two distinct memory systems during spatial learning.

Disclosures: N.T. Reitz: None. **J.L. Vincze:** None. **J.B. Hales:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 710.01/TT42

Topic: H.01. Animal Cognition and Behavior

Support: CIHR

NSERC

Title: The effect of eye movements and gaze on hippocampal activity in non-human primates in virtual environments

Authors: *B. W. CORRIGAN[1], R. A. GULLI[1], G. DOUCET[2], J. C. MARTINEZ-TRUJILLO[1]
[1]Physiol. and Pharmacol., Univ. of Western Ontario, London, ON, Canada; [2]McGill Univ., Montreal, QC, Canada

Abstract: Exploration of the environment differs significantly between rodents and primates: while rodent exploration is largely multisensory, primates rely heavily on their highly-developed vision to look at their immediate surroundings and more distant locations. While place-like cells have been found in primates exploring real and virtual environments (Ono et al., J Neurophys., 1993; Matsumura et al., J Neurosci., 1999), cells encoding eye position as well as gaze location have been found in the hippocampus (Ringo et al., J Neurophys., 1994; Georges-François & Rolls, Cerebral Cortex, 1999), and entorhinal cortex recordings have found saccade direction cells (Killian et al. PNAS 2015). To further test and disambiguate the selectivities of hippocampal units, we trained two male *Macaca mulatta* to do a cued saccade task and two different tasks in a virtual environment. We recorded single units within the right hippocampus. We tracked the eye movements, and classified them into saccades and foveations. We then analyzed firing rate selectivities of units for saccade direction, target screen location, target world location and place in the environment. Using non-parametric analyses to determine selectivity. We found that while some units showed selectivity for saccade direction or screen location, these selectivities did not carry over to other tasks. Using a virtual environment allowed us to record the virtual position of the subject, as well as the gaze location in three dimensions of each foveation in the environment. We binned space in the virtual environment, and will ran analyses to test selectivity of a neuron for position and gaze location. This research will help characterize the encoding that happens in the primate hippocampus.

Disclosures: B.W. Corrigan: None. **R.A. Gulli:** None. **G. Doucet:** None. **J.C. Martinez-Trujillo:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 710.02/TT43

Topic: H.01. Animal Cognition and Behavior

Support: Sacramento State Research and Creative Activity Faculty Awards Program

Title: Head direction cell instability in the anterior dorsal nucleus of the thalamus following intraseptal microinfusions of the $GABA_A$ agonist muscimol

Authors: *I. PASTOR, C. P. CERVANTES ALDANA, M. Y. HURTADO, J. L. CALTON
Psychology, California State Univ., Sacramento, CA

Abstract: Head direction (HD) cells, found in many regions of the rat Papez circuit, are believed to reflect the animal's directional orientation and are thought to play a critical role in navigation. Previous studies have shown that septal infusions of the $GABA_A$ agonist muscimol eliminates hippocampal theta activity (Givens & Olton, 1990), leads to a decrement in the positional signal carried by place cells, and produces navigational deficits (Brazhnik, Muller, & Fox, 2003). Interestingly, the pathways that mediate the hippocampal theta rhythm bear a remarkable similarity to the adjacent nuclei mediating head direction signals (Taube, 1998), and neurons possessing both HD and theta properties have been identified in the two nuclei mediating the HD generative circuit (Stackman & Taube, 1998). More recent studies have demonstrated the existence of theta modulated HD signals in some, but not all areas known to contain HD cells; however, little has been done to examine the influence of theta oscillations on HD cells in their most abundant location, the anterior dorsal nucleus of the thalamus (ADN). Given the relationship between the hippocampal theta rhythm and the location-specific firing of place cells, and findings that indicate an interrelationship between place cells and HD cells, it is likely that the HD system may also be associated with theta. Thus, the present investigation sought to characterize the effects of reversibly inactivating the medial septum using microinjections of the $GABA_A$ agonist muscimol on (1) the basic directional characteristics of ADN HD cells, (2) the ability of HD cells to shift their preferred direction following visual landmark rotation, and (3) the maintenance of a stable preferred firing direction using idiothetic cues in darkness. EEG recordings were made before and after inactivation of the medial septal area, and hippocampal theta power was significantly reduced following inactivation. In the landmark rotation experiment, intraseptal administration of muscimol produced a population of HD cells with preferred directions that shifted unpredictably between sessions, suggesting that cue control was affected. Further, following septal inactivation a significant population of HD cells was unable to maintain a stable preferred firing direction when the animals locomoted in the dark, suggesting that idiothetic cue processing was affected. These findings suggest that theta oscillations are necessary to maintain the directional stability of HD cells in anterodorsal thalamus.

Disclosures: I. Pastor: None. **C.P. Cervantes Aldana:** None. **M.Y. Hurtado:** None. **J.L. Calton:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 710.03/TT44

Topic: H.01. Animal Cognition and Behavior

Title: Galantamine potentiates neuroprotective effect of taurine & coenzyme Q 10 & their interaction against Aβ (1-42) induced cognitive dysfunction

Authors: *A. SINGH, A. KUMAR
Panjab Univ., Chandigarh, India

Abstract: Background: Taurine, 2-aminoethanesulfonic acid, acts as a neuromodulator, prevent mitochondrial dysfunction, apoptosis and oxidative stress. Also prevent the neurotoxicity of amyloid beta peptide [(Aβ) (1-42)] by binding on $GABA_A$ receptor. Coenzyme Q 10 (CoQ10), a lipophilic, endogenous, vitamin-like antioxidant compound. It has been reported to improve cognition, restored mitochondrial function and facilitates ATP synthesis.
Aim: We aimed to evaluate the neuroprotective effect of galantamine on taurine and CoQ10 and their interaction in Aβ (1-42) induced cognitive dysfunction in rats.
Materials and methods: Intrahippocampal (*i.h.*) Aβ (1-42) (1µg/µl; 4µl/site) were administered, followed by drug treatment with taurine (25, 50 and 100 mg/kg), CoQ10 (10 and 20 mg/kg) galantamine (2 mg/kg) and their combinations for a period of 21 days. Various neurobehavioral parameters followed by biochemical, AChEs level, mitochondrial enzyme complex level (I-IV), TNF-α level, neurotransmitter level and histopathological alterations were assessed.
Results: Administration of Aβ (1-42) significantly impaired cognitive performance in Morris water maze (MWM) test, causes oxidative stress, raised AChEs level, neurotransmitter levels, neuroinflammation, mitochondrial dysfunction and alterations in histopathology as compared to sham treatment. Treatment with taurine (25, 50 and 100 mg/kg), CoQ10 (10 and 20 mg/kg) and galantamine (2 mg/kg) significantly improved the cognitive performance as evidenced by reduced transfer latency and increased time spent in the target quadrant in MWM test, reduced AChEs activity, neuroinflammation, oxidative damage (reduced LPO level
and restored SOD and GSH levels), TNF-α level, restored mitochondrial respiratory enzyme complex (I-IV) activities, histopathological alterations and neurotransmitter levels as compared to Aβ (1-42) treated animals. Further, combinations of taurine (25 and 50 mg/kg) and CoQ10 (10 and 20 mg/kg) with galantamine (2 mg/kg) significantly modulate the neuroprotective potential of taurine in Aβ (1-42) treated animals.
Conclusion: The present study suggests the neuropotentiating effect of galantamine on taurine and CoQ 10 as indicated by improved behavioral parameters, oxidative stress, AChEs levels, TNF-α level, mitochondrial functions, neuroinflammation, neurotransmitter levels and histopathological alterations.

Disclosures: **A. Singh:** None. **A. Kumar:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 710.04/TT45

Topic: H.01. Animal Cognition and Behavior

Support: NIH U01-NS090583

NSF PRAC 1614622

Title: Determinants of sparse population coding in a computational model of the rat dentate gyrus

Authors: ***I. RAIKOV**[1], A. D. MILSTEIN[3], I. SOLTESZ[2]
[2]Sch. of Med., [1]Stanford Univ., Stanford, CA; [3]Neurosurg., Stanford Univ. Sch. of Med., Stanford, CA

Abstract: The hippocampus provides the basis for spatial navigation and episodic memory in the brain, remembering events experienced in the past and linking them with their spatio-temporal context (O'Keefe and Nadel, 1978). The dentate gyrus (DG) is one of the major subfields of the hippocampus, with excitatory input arriving from Layer II of the entorhinal cortex (EC). The principal cells of the dentate gyrus are the granule cells (GCs). The cellular and circuit characteristics of the dentate gyrus combine uniquely to constrain the number of active GCs in order to maintain sparse population activity. GCs receive strong inhibition from local GABAergic interneurons (INs), however, a very conspicuous feature of the dentate circuitry is that GCs also receive direct excitatory glutamatergic input from mossy cells (MCs) . One of the great enigmas of the hippocampus, the net effect of MC input on GCs, is a topic of active research, as mossy cells also activate local INs that inhibit the GC population, and the resulting balance of inhibition and excitation has not yet been fully understood (Danielson et al., 2017, GoodSmith et al. 2017, and Sensai and Buzsáki, 2017). In the present study, we used a full-scale, data-driven computational model of the rat DG to investigate the role of MC and different IN populations in the encoding of realistic spatial trajectory input. By applying entorhinal stimuli that mimicked grid cell path trajectories and perturbing the connections and properties of different cell types, we found that GC responses were modulated by all IN classes differentially, and were able to form distinct place fields in response to largely overlapping simulated grid cell patterns. However, when our model was configured with the connectivity distributions developed for previous versions of the model (Dyhrfjeld-Johnsen et al., 2007), we were unable to replicate the results of recent experimental results, which have suggested that mossy cells have multiple place fields, higher peak firing rates, and robust spatial remapping. This has led us to

implement revisions to the model such that molecular layer perforant pathway (MOPP) interneurons have an increased role in feedforward inhibition of GCs (Li et al., 2013), and such that hilar perforant pathway (HIPP) interneurons have an increased role in feedback inhibition of GCs. With these revisions, the GC and MC model cells were able to achieve firing rates and place field characteristics consistent with recent experimental studies. In summary, our results suggest several important avenues for further investigation of the mechanisms that underlie sparse coding in the dentate gyrus.

Disclosures: I. Raikov: None. **A.D. Milstein:** None. **I. Soltesz:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 710.05/TT46

Topic: H.01. Animal Cognition and Behavior

Title: Neural correlates of goal representations and planning in a multi-step navigation task

Authors: *N. ZARR[1], J. W. BROWN[2]
[1]Psychological and Brain Sci., [2]Indiana Univ., Bloomington, IN

Abstract: A primary aim of cognitive control research is to understand how people organize their behavior in pursuit of goals. In many contexts, goal information needs to be maintained across an extended period of behavior, but the neural substrate of this information is uncertain. Complicating matters, multiple subgoals often need to be reached before a final goal can be achieved.
Past studies using univariate analyses have implicated a variety of regions including dorsolateral prefrontal cortex (DLPFC) and parietal cortex in goal representation, planning, and goal execution. Multi-voxel pattern analysis (MVPA) provides a complementary set of evidence by asking which groups of voxels contain information about a particular condition, including goal identity. Past MVPA studies revealed different substrates for maintained sensory information in working memory tasks versus those identified by univariate analyses, with sensory cortex representing sustained modality-specific information.
Human subjects performed a multi-step planning task while being scanned with fMRI. We asked which regions are responsible for representing final and intermediate goal states, using MVPA to identify the loci of representations. A secondary question concerned the degree to which patterns of neural activity instantiating a goal are similar to the patterns elicited when that state is finally reached.
We found evidence that perceptual coding can be extended to representations of goals in a spatial navigation task. A searchlight analysis demonstrated that the identity of a goal state could be decoded with significantly above-average accuracy from visual cortex, both for intermediate and

final goals, but not from other regions including DLPFC.
Overall, our results suggest that functions previously attributed more to frontal regions, such as goal directed behavior and planning, may instead depend more heavily on primary sensory cortical regions.

Disclosures: N. Zarr: None. **J.W. Brown:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 710.06/TT47

Topic: H.01. Animal Cognition and Behavior

Support: SFN-IBRO, 2017 Travel Grant

Title: Neuroprotective effects of quercetin loaded nanoconstructs in murine neurocognitive model

Authors: *C. SINGH
Univ. Inst. of Pharmaceut. Sci., Panjab Univ., Chandigarh, India

Abstract: In the present study, Formulation by Design (FbD) enabled lipidic nanostructured system were formulated for quercetin (Q-NLCs). They were evaluated for their efficiency in nose-to-brain targeting and biodistribution in a suitable animal model after intranasal delivery. Further, particles size characterization revealed the particle size in the nano range. Stability studies indicated refrigeration found to be the preferred storage condition. FTIR, DSC, PXRD and SEM studies revealed formation of less ordered crystalline structure of lipid matrix favouring higher encapsulation of quercetin. *In vitro* antioxidant performance was improved after encapsulation in nanolipidic carriers. Moreover, the biochemical profile of brains of the animals receiving the drug in the form of Q-NLCs was close to that of the normal animals. Aluminium chloride was able to induce reduction in GSH levels only upto 53.98 ±3.51% in the group of animals receiving plain quercetin as the drug. On the other hand, the Q-NLCs were able to significantly resist the decrease in reduced GSH levels ($p < 0.05$). Similarly, the treatments were able to resist brain MDA levels increase in the group receiving Q-NLCs compared to free quercetin alone ($p < 0.05$). Further, the higher %drug targeting efficiency (%DTE) and drug transport percentage (DTP) were observed for Q-NLCs vis-à-vis free quercetin. Hence, the current investigation demonstrates the potential of nano-antioxidant as a potent therapeutic intervention for HIV associated neurocognitive disorders with improved biopharmaceutical attributes.

Disclosures: C. Singh: None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

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Program#/Poster#: 710.07/TT48

Topic: H.01. Animal Cognition and Behavior

Support: Howard Hughes Medical Institute

DFG PF714/4-1

Title: Calcium imaging in tethered behaving honeybees

Authors: *M. HELD[1], L. LAVIS[1], V. JAYARAMAN[1], K. PFEIFFER[2]
[1]HHMI Janelia Res. Campus, Ashburn, VA; [2]Biocenter Univ. of Wuerzburg, Wuerzburg, Germany

Abstract: Honeybees have a remarkable repertoire of complex sensory-guided decision-making behaviors like adaptive navigation based on terrestrial landmarks and sky-compass cues. These abilities have been demonstrated in a number of behavioral studies. The neural circuits implicated in navigation in other insects — pathways leading to and including a region called the central complex — have also been traced and identified anatomically in bees (Zeller et al. 2015, Held et al. 2016). Studies that probe the physiology of the involved brain regions have used calcium imaging of neurons in the anterior optic tubercle — a region known to be involved in the sky-compass pathway of other species (Pfeiffer et al. 2005) — in completely fixed bees (for example, Mota et al. 2013). In addition, multi-site local field potential recordings have been performed in the optic lobes of tethered walking bees (Paulk et al. 2014). We seek to combine the strengths of these approaches in a paradigm that establishes stable, targeted two-photon calcium imaging in the brain of tethered behaving honeybees walking on an air-supported ball. The movements of the bee on the ball are used to move visual patterns on a surrounding virtual reality arena giving the bee closed-loop control of its visual environment. For calcium imaging, we label populations of neurons using bulk loading of a new generation of synthetic calcium sensors that are masked with acetoxymethyl esters to minimize the damage of these neurons. We are specifically targeting brain regions that are likely involved in landmark and sky-compass navigation based on work in other insects (Pfeiffer and Homberg 2014, Seelig and Jayaraman 2015). These regions include the anterior optic tubercles, the bulbs, and the central complex. We will discuss our ongoing efforts to record the physiological responses of neurons in these regions during different tasks like single or multiple stripe fixation and object discrimination. Ultimately, we hope to use the paradigm to probe neural functions of honeybees during navigational behavior, but this technical advance will also open-up the possibility of studying a wider range of compelling questions relating to decision-making and memory.

Disclosures: **M. Held:** None. **L. Lavis:** None. **V. Jayaraman:** None. **K. Pfeiffer:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 710.08/TT49

Topic: H.01. Animal Cognition and Behavior

Support: Howard Hughes Medical Institute

Title: How the ultrastructure of the fly compass circuit shapes its dynamics

Authors: S. ALI, A. SHERIDAN, T. PATERSON, R. FRANCONVILLE, D. B. TURNER-EVANS, S. WEGENER, T. WOLFF, J. S. LAURITZEN, D. BOCK, *V. JAYARAMAN
Janelia Res. Campus, HHMI, Ashburn, VA

Abstract: The central complex (CX) is a highly conserved brain region implicated in spatial navigation in insects. The region comprises several neuropils, including the protocerebral bridge (PB), ellipsoid body (EB), and the paired noduli (No). Physiological recordings from populations of identified CX neurons have revealed compass-like neural dynamics, including a localized "bump" of persistent activity in the donut-shaped EB that tracks the fly's orientation in visual surroundings and in darkness. In particular, the anatomy and activity of two specific populations of columnar neurons, E-PG and P-EN neurons, suggest they are connected in a recurrent loop that helps maintain and move the activity bump in response to rotations of the fly (Turner-Evans*, Wegener* et al., eLife, *in press*). The gross morphology of E-PG and P-EN neurons is stereotyped, with each individual neuron connecting a specific wedge of the donut-shaped EB with a single column of the handlebar-shaped PB. Light-level analysis suggests that the E-PG neurons send their axons to the PB and their dendrites to the EB, while the P-EN neurons appear to have complementary dendritic and axonal innervation patterns. Now, using high-throughput transmission electron microscopy of serial thin-sections of a complete fly brain, we have reconstructed several of these and other CX neuron types to map their synaptic connectivity. We discovered that, in addition to the PB-EB recurrent loop between E-PG and P-EN neurons, these neurons are also densely and recurrently connected within the EB. We are now analyzing how this local recurrence influences attractor dynamics in the structure. Connectivity in the PB was more complex still, with wide-field interneurons mediating connectivity between E-PG and P-EN neurons. In addition to relating the anatomy of these neurons to physiology, we will describe our efforts to use compartmental modeling to understand what role these structural motifs and synaptic connections play in the generation, maintenance and propagation of compass-like activity in the circuit.

Disclosures: **S. Ali:** None. **A. Sheridan:** None. **T. Paterson:** None. **R. Franconville:** None. **D.B. Turner-Evans:** None. **S. Wegener:** None. **T. Wolff:** None. **J.S. Lauritzen:** None. **D. Bock:** None. **V. Jayaraman:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 710.09/TT50

Topic: H.01. Animal Cognition and Behavior

Title: Understanding neural activity and behavior during visual learning in *Drosophila*

Authors: *C. DAN, J. WITTENBACH, A. HERMUNDSTAD, V. JAYARAMAN
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Abstract: Many animals, including *Drosophila melanogaster*, can effectively navigate their visual environment to search for food, find conspecifics, and avoid predators. It is also critical to their survival to be able to adjust their navigational strategies based on past experience, for example, by remembering the negative or positive consequences of being in specific visual surroundings. However, the neural circuit mechanisms that enable animals to make such associations and thereafter modify their behavior are not yet fully understood. *Drosophila* can associate visual patterns with a heat punishment in a flight simulator, remember the location of a cool spot in an otherwise hot environment using visual place learning, and associate color or light intensity with a reward or punishment. Combined with precise genetic access to various cell types, this offers an opportunity for detailed mechanistic understanding of adaptive visual navigation.

To understand the behavioral logic of visual learning, we analyzed the actions of head-fixed flying *Drosophila melanogaster* in a closed-loop visual virtual reality environment in which changes in their wingbeats were used to control the angular rotation of a visual scene. Similar to flight simulator learning reported previously, the flies were trained to associate visual patterns (conditioned stimulus, CS) with a heat punishment (unconditioned stimulus, US) delivered by an infrared laser pointed at their back. We found that their flight actions underwent coordinated changes through training, and that these changes were highly correlated to their learning performance. We are constructing an empirically informed model using a reinforcement learning framework to quantitatively characterize such moment-to-moment correlations between visual stimuli and the fly's actions.

To investigate the neural mechanisms underlying changes in the fly's behavior, we also monitor the activity of specific neural populations using two-photon calcium imaging during this task. We have identified neural activity correlated to the negative reinforcement, flight action, and visual orientation in the central complex, a region implicated in visual navigation in the fly, and

we are investigating these neural responses before, during and after training. In the long term we hope to use a model-driven approach to establish causal links between neural circuit activity and changes in the fly's decision-making over the course of visual learning.

Disclosures: C. Dan: None. **J. Wittenbach:** None. **A. Hermundstad:** None. **V. Jayaraman:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

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Program#/Poster#: 710.10/TT51

Topic: H.01. Animal Cognition and Behavior

Support: NEI R01EY022062

ONR N000141110525

Title: Monkey Hippocampal

Authors: *W. K. PAGE, C. J. DUFFY
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Abstract: Hippocampal place cell activity is linked to the animal's location in navigational space, in both rodents (O'Keefe and Dostrovsky, 1971) and old world monkeys (Hori, et. al, 2003). This activity is modulated by the hippocampal local field potential's theta rhythm in rodents (O'Keefe and Recce, 1993), with hippocampal theta linked to saccadic visual exploration in monkeys (Jutras, et. al, 2013). We have now examined potential links between saccades, theta, and hippocampal place cell activity in our continuing studies of cortical-hippocampal interactions in monkeys.
We trained a Rhesus monkey to actively steer its real self-movement through a lighted room. Movement trials begin with the monkey glancing down at a small video display that briefly indicated the monkey's current room location and the next target room location. The monkey used an X-Y joystick to steer a continual path through the room across successive target room locations. The monkey received liquid reward on its arrival at each target location.
During real self-movement, we recorded single neuron activity and local field potentials (LFPs) from microelectrodes placed in medial superior temporal (MST) extrastriate visual cortex, and in the hippocampus. These signals were combined with magnetic search coil eye position records, and with sled interface mediated joystick deflection, room location, and sled movement records. MST neurons showed direction sensitive, self-movement related activity like that attributed to visual and vestibular integration in earlier studies (Page and Duffy, 2003; Fetsch, et al., 2010). This activity showed discrete pauses during saccadic eye movements as the monkey explored its

continually changing view of the room. Hippocampal neurons showed room location related activity with discrete pauses related to increases in theta power associated with its approaching the target room location. In some neurons, theta effects were seen in MST and saccade effects were seen in the hippocampus.
Our findings suggest that cortical self-movement analysis may be projected to the hippocampus, and hippocampal place analysis may be projected to MST cortex. Cortical-hippocampal interactions may create a network supporting navigation and spatial orientation.

Disclosures: W.K. Page: None. **C.J. Duffy:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 710.11/TT52

Topic: H.01. Animal Cognition and Behavior

Support: CIN, Excellence Initiative EXC 307

Deutsche Forschungsgemeinschaft (DFG) BU 3126/1-1

Title: Biasing head-direction activity of single presubicular neurons by juxtacellular stimulation

Authors: *S. COLETTA[1,2], M. FREY[1], K. NASR[1,2], P. PRESTON-FERRER[1], A. BURGALOSSI[1]
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Abstract: In order to support navigation, the firing of head-direction (HD) neurons must be tightly anchored to the external space. Indeed, inputs from external landmarks can rapidly reset the preferred direction of HD cells. Landmark stimuli have often been simulated as excitatory inputs from ‘visual cells’ (encoding landmark information) to the HD attractor network; when excitatory visual inputs are sufficiently strong, preferred directions switch abruptly to the landmark location.
In the present work, we tested whether mimicking such inputs via juxtacellular stimulation would be sufficient for shifting the tuning of individual presubicular HD cells, recorded in passively-rotated rats. We found that in a cue-rich environment, HD activity was remarkably stable; evoking spikes outside the preferred direction did not lead to significant changes in HD tuning. However, when the number of available landmarks was reduced to a single proximal cue, the large majority of HD cells showed a drastic reduction in HD tuning and stability. Under these conditions, single-cell stimulation induced a spiking bias at the stimulus location. We propose

that, under conditions of HD cell instability, single-cell stimulation can be sufficient for anchoring HD activity.

Disclosures: S. Coletta: None. **M. Frey:** None. **K. Nasr:** None. **P. Preston-Ferrer:** None. **A. Burgalossi:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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Support: European Research Council grant no. 282091 - DEVSPACE

BBSRC grant BB/I021221/1

Royal Society grant UF150692

Title: Coherence and stability of head direction cells in an open-loop state in pre-eye opening rat pups

Authors: *J. P. BASSETT[1], T. J. WILLS[2], F. CACUCCI[1]
[1]Neuroscience, Physiology, and Pharmacol., [2]Cell and Developmental Biol., Univ. Col. London, London, United Kingdom

Abstract: Head direction (HD) cells fire as a function of an animal's directional orientation in its environment. One of several classes of spatially modulated neuron, they are found in a variety of hippocampus-connected sites and are believed to be fundamental for the neural representation of space in the brain. During development, HD cells precede other spatially tuned cell types in maturation, reaching adult levels of spatial tuning by post-natal day 16 (P16). To date, HD cells have been recorded in rat pups as early as P12, up to 3 days before eye opening. Prior to eye opening, HD cell firing is characterised by low spatial information content and directionally unstable firing. Both Spatial firing characteristics improve with age, and a sharp increase in the number of HD cells, their information content, and their stability occurs around after eye opening.To test whether pre-eye opening HD cells can be stabilised by altering sensory cues, we recorded ADN neurons whilst while rat pups explored an environment much smaller than used in previous studies (20cm side square). In this smaller box, we observe HD cells with adult-like directional tuning and stability from P13 onwards. In a standard recording environment (60cm side square), directional tuning of the same HD cells is poor or non-existent. Nonetheless, on a short time scale, the separation angles between HD cell pairs' firing are fully preserved in the large environment. This suggests that a coherent and robust internal representation of space is present from P13, and that impaired directional tuning results from the drift of the ensemble with

respect to the external environment. To investigate the precise nature of the drift and its origin, we used the known offset angles of the HD cells in the small box to perform standard Bayesian decoding of signalled direction in the large environment. We find that signalled direction slowly drifts with respect to true direction, in a manner consistent with under-signalling of angular head velocity. This pattern of velocity under-signalling is consistent with the open-loop state of the vestibular signal before visual feedback becomes available upon eye opening. We conclude that the internal structure of the HD cell network is adult-like before eye opening, but that it will operate in an open-loop mode until vision, or alternative sensory feedback modalities, are available.

Disclosures: **J.P. Bassett:** None. **T.J. Wills:** None. **F. Cacucci:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: ISF #955/13

ISF #1882/13

Rappaport Institute grant

Allen and Jewel Prince Center for Neurodegenerative Disorders of the Brain grant

Title: Egocentric border cells upstream of the entorhinal cortex

Authors: X. GOFMAN[1], S. WEISS[2,1], S. RAPOPORT[1], *D. DERDIKMAN[1]
[1]Technion - Israel Inst. of Technol., Haifa, Israel; [2]Tel-Aviv Univ., Tel-Aviv, Israel

Abstract: The hippocampal formation encompasses populations of spatially selective cells, which form together an internal cognitive map. It is hypothesized that the input to those areas is generated mainly from self-motion and visual cues in an egocentric (self-centered) reference frame, which are then transformed to an allocentric (world-centered) reference frame downstream in the hippocampal formation. An important question is how the transition between those two references frames occurs. In order to answer this question, we recorded cells in V2 and the postrhinal cortex (POR), upstream of the entorhinal cortex, in awake behaving rats while they were performing a random foraging task.
Our hypothesis is that there are cells with egocentric spatial properties in the POR, which function as an input source for border cells. So far, our data shows a new type of cell that has a selectivity to the borders of the arena in egocentric coordinates. This type of egocentric border

cell fires when the wall is at a given orientation relative to the rat, in an egocentric coordinate frame. Our results suggest that these egocentric border cells are the generators of allocentric border cells downstream in the entorhinal cortex. Thus, we show here a candidate for generation of spatially selective cells, upstream of the hippocampal formation.

Disclosures: **X. Gofman:** None. **S. Weiss:** None. **S. Rapoport:** None. **D. Derdikman:** None.

Poster

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Topic: H.01. Animal Cognition and Behavior

Support: 1R01MH100631

Title: *In vivo* Imaging of entorhinal inputs to hippocampal area CA1 in behaving mice

Authors: *J. BOWLER[1], A. LOSONCZY[2]
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Abstract: The hippocampus is thought to be a critical for the storage of episodic memories and contextual representations with the primary cortical source of input to the hippocampus being the Entorhinal Cortex (EC). The EC is split into medial (MEC) and lateral (LEC) regions with the former thought to primarily represent spatial aspects of context and the later representing non-spatial aspects. The EC is known to send projections to the hippocampus through via the perforant pathway to the CA1 subregion. Hippocampal place cells remap rapidly when exposed to new environments and are known to persist between multiple exposures to the same environment. However, the precise nature of information carried by MEC and LEC inputs remain unknown. Using two-photon imaging combined with virally targeted Ca2+ indicators we observed and characterized activity in MEC and LEC axonal projections to the hippocampal area CA1 in mice. Through the use of head-fixed virtual reality navigational tasks performed on a custom setup it is possible to image activity in MEC and LEC axonal projections while presenting and switching visual, olfactory and auditory contextual cues. Our initial results indicate that projections from MEC carry some degree of spatial information during head-fixed naviagation. Future experiments aim to characterize the nature of the spatial and non-spatial information originating from MEC and LEC and to classify distinctions between the projections originating in both LEC and MEC.

Disclosures: **J. Bowler:** None. **A. Losonczy:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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Program#/Poster#: 710.15/TT56

Topic: H.01. Animal Cognition and Behavior

Title: Oscillatory dynamics in the limbic thalamo-cortical network reveal subcortical information flow to and from the hippocampal formation

Authors: *G. VIEJO[1], G. BUZSAKI[2], A. PEYRACHE[3]
[1]Montreal Neurolog. Inst., Univ. McGill, Montreal, QC, Canada; [2]New York University, Sch. of Med., New York, NY; [3]Montreal Neurolog. Inst., McGill Univ., Montreal, QC, Canada

Abstract: The thalamus relays sensory signals to the cortex, but also between cortical areas. These networks exhibit a wide range of oscillatory dynamics, modulated by various factors such as brain states and attentional recruitment. These interactions arise from a combination of feed-forward (thalamo-cortical) and feedback (cortico-thalamic) controls. The sensory and motor components of these networks, involving the posterior thalamus, have been widely studied *in vitro* as well as *in vivo* models. In contrast, the anterior part of the thalamus is a key part of the limbic system: it receives subthalamic inputs from the mammillary bodies, and is reciprocally connected with the hippocampal formation and the midline cortex. These thalamo-cortical networks are essential for navigation and memory formation, among other limbic-related functions, yet they have only been poorly characterized *in vivo* so far. To further our understanding of these networks, we collected thalamo-hippocampal and thalamo-cortical neuronal ensembles and Local Field Potentials (LFP) during freely moving behavior and sleep. We show that thalamic nuclei of the anterior thalamus, including the antero-dorsal (AD), antero-ventral (AV), and antero-medial (AM), can be discriminated on the basis of their influence on, or entrainment by hippocampal and cortical activity. In particular, thalamic neurons were differentially modulated during non-REM sleep by the thalamo-cortical slow waves (the fluctuation between DOWN and UP states) and the hippocampal sharp-waves ripples (SWRs). The onset of UP states in AD precedes UP states in neighboring nuclei by up to 100ms. The late-onset neurons in AV and AM were strongly responsive to SWRs and were generally highly modulated by theta oscillations during wakefulness and REM sleep. These results suggest that AD neurons, which transmit a signal related to head-direction to cortical and hippocampal areas, may play a key role in activating downstream targets. In contrast, other anterior thalamic nuclei are mainly driven by cortical and hippocampal feedback and may play a key role in transmitting hippocampal outputs to other cortical areas.

Disclosures: G. Viejo: None. **G. Buzsaki:** None. **A. Peyrache:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: McGill University starter grant

Sir Henry Wellcome Postdoctoral Fellowship

Title: Thalamic processing of the head-direction signal

Authors: *A. J. DUSZKIEWICZ, D. WANG, A. PEYRACHE
Montreal Neurolog. Inst. and Hosp., McGill Univ., Montreal, QC, Canada

Abstract: As we navigate the world, it is crucial to maintain a robust sense of where we are. Head-direction (HD) cells serve as the brain's internal 'compass' and each of them is tuned to the specific direction the animal is facing, independently of its location and ongoing behavior. The anterodorsal thalamic nucleus (AD) is a key relay of the HD signal. AD neurons seem to be reciprocally connected with the reticular nucleus (TRN) - an inhibitory thalamic nucleus believed to control the routing of sensory information. Recurrent inhibition is important in shaping attractor network dynamics and it may select subsets of neurons coding for the same direction. Therefore, although the HD signal itself may originate from subthalamic nuclei, the AD-TRN system may play a central role in its processing. Still, connectivity and functional importance of the AD-TRN circuit remain elusive. In order to characterize the functional significance of the AD-TRN circuit, we used a combination of high-density single unit recordings and projection-specific optogenetic interrogation in freely moving mice. Preliminary results show that optogenetic TRN stimulation leads to uniform inhibition of HD cells in AD at short latency, which in turn indicates monosynaptic inhibitory connection. Further experiments using selective optogenetic inactivation of AD to TRN and TRN to AD projections will determine whether thalamic inhibition plays a role in shaping the attractor dynamics of thalamic HD cells.

Disclosures: A.J. Duszkiewicz: None. **D. Wang:** None. **A. Peyrache:** None.

Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NSF-ANR CRCNS #1429937

Title: Topological map learning during preexposure and replay as an explanation of latent learning

Authors: P. SCLEIDOROVICH[1], M. LLOFRIU ALONSO[2], N. CAZIN[3], B. HARLAND[4], P. F. DOMINEY[5], J.-M. FELLOUS[6], *A. WEITZENFELD[2], *A. WEITZENFELD[2]
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Abstract: In Blodgett's (1929) experiments, rats that were pre-exposed to a maze without rewards were able learn a task on that maze faster. This phenomenon was named latent learning. In this work we present a model of Blodgett's multiple-T maze experiments. Our model updates intra-hippocampal synaptic weights during pre- exposure trials. During the task, those weights are used to generate replay events that drive off-line learning. We show that pre-exposed artificial rats are able to learn the task significantly faster, validating the hypothesis of the model. We also show that the effect is increased with the number of pre-exposed trials and replay events per trial. We also present an analysis of the shortcomings of this replay model and propose possible solutions. This work is part of our current project on assessing the role of the intra-hippocampal synapse modulation in tasks reminiscent of the "Traveling Salesperson Problem" (TSP), where rats have to optimize their navigation to multiple rewarded feeders.

Disclosures: P. Scleidorovich: None. **M. Llofriu Alonso:** None. **N. Cazin:** None. **B. Harland:** None. **P.F. Dominey:** None. **J. Fellous:** None. **A. Weitzenfeld:** None. **A. Weitzenfeld:** None.

Poster

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Program#/Poster#: 710.18/TT59

Topic: H.01. Animal Cognition and Behavior

Title: Extracting grid and border components from field potentials in hippocampus and entorhinal cortex

Authors: *S. MACKESEY[1], M. MATENA[2], F. T. SOMMER[3]
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Abstract: Advances in recording technology driven by large-scale neuroscience projects (e.g. BRAIN initiative, Human Brain Project) promise to deliver unprecedented high-resolution recordings of brain activity. In particular, extracellular arrays with hundreds to thousands of electrodes are generating high-dimensional field potential ("FP") datasets. There are significant advantages to decoding behavioral information from FPs (as opposed to spikes) but the information encoded in FPs is still poorly understood. One successful approach to FP analysis and decoding is as follows: (1) filter to a band of interest; (2) apply unsupervised learning methods to the filtered data; (3) assess the correlation of learned features with stimulus, behavioral, or other physiological variables using supervised learning methods. This approach has revealed that theta-filtered hippocampal FPs recorded in hippocampal subregions CA1 and CA3 encode the location of a navigating rat. Decomposition of these FPs into independent components yields components tuned to specific locations ("featured-tuned field potentials", or "FFPs"), analogous to place cells. Here we investigate whether other functional cell types in hippocampus and entorhinal cortex, such as grid cells, head direction cells, and border cells, also have corresponding FFP components. Our results show that this is indeed the case. We further examine the spatial patterns of the discovered FFPs with respect to hippocampal anatomy. To quantify the relationship between field potentials, spikes, and spatial variables we use linear decoding and mutual information analysis. We analyze various experimental datasets varying in the subject, number and location of electrodes, and experimental task.

Disclosures: S. Mackesey: None. **M. Matena:** None. **F.T. Sommer:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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Support: CIHR Project Grant #367017

Brain Behaviour Research Foundation #23723

Canada Research Chair Program

Title: Hippocampal subregion CA1 requires CA3 input to encode novel space

Authors: *I. SHANK[1], M. P. BRANDON[2]
[1]Integrated Program in Neurosci., [2]Psychiatry, McGill Univ., Montreal, QC, Canada

Abstract: Substantial work on the entorhinal-hippocampal circuit has revealed a myriad of spatially tuned neurons, yet the details on how these cell types interact and generate new codes for novel space remain limited. Our prior work has argued against a grid-to-place cell

feedforward transfer model, whereby region CA1 requires entorhinal grid cell input to establish new spatial maps. Here, we explore the possibility that the CA1 place code relies on previously generated assemblies, or maps, that are stored within the CA3 auto associative network. Previous work has assessed and rejected this possibility in familiar environments, however we suggest that transfer of information from CA3 to CA1 would be most critical as animals initially establish a spatial map when exploring a novel environment. To examine this, we used a chemogenetic approach in Grik4-cre transgenic mice to silence CA3 neurons while animals were introduced to a novel environment. We first assessed the effect of CA3 inactivation on the entirety of CA1 by conducting cfos immune-labelling approach. A cre-dependent AAV that expresses the hM4di inhibitory DREADD was injected into CA3 of Grik4-cre mice. The hM4di receptor is activated upon binding of its ligand, Clozapine-N-Oxide (CNO). Mice were then injected with either 1) saline, 2) 1 mg/kg of CNO, or 3) 10 mg/kg of CNO, 40 minutes prior to exposure to a $90cm^2$ novel open field for 20 mins. We observed a CNO dose-dependent decrease in cfos labelling across the entire hippocampal CA1 population compared to control mice. In a second approach, we performed chronic *in vivo* recordings of CA1 neurons in CA3 hM4di expressing Grik4-cre mice. Prior to CNO injection, a baseline recording was taken in a $90cm^2$ familiar open field (F1). Forty minutes after a 5 mg/kg CNO or saline injection was administered mice were exposed to a novel environment (N1), the familiar environment (F2) and again the novel environment (N2). Recovery recordings were obtained from the familiar (F3) and novel (N3) environments 12 hours after injection. Preliminary data indicates that CA1 neurons fail to form discrete place fields in the absence of CA3 input in N1 & N2. We also observed a reduction of place cell stability and increased field size in F2. These results suggest that information flow from CA3 to CA1 pyramidal cells is a prerequisite to build and sustain CA1 spatial maps. We propose that the auto associative capacity of CA3 enables it to store pre-existing cell assemblies to be used for encoding new information. Further work is needed to validate these ideas and to determine whether pre-existing networks in CA3 support coding beyond the spatial realm to facilitate one-shot learning and episodic memory.

Disclosures: I. Shank: None. **M.P. Brandon:** None.

Poster

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Topic: H.01. Animal Cognition and Behavior

Support: CIHR Project Grant #367017

Brain Behavior Research Foundation #23723

Canada Research Chairs Program

Title: Investigation of the head direction signal in the anterodorsal thalamic nucleus using miniaturized microscopes in behaving mice

Authors: *Z. AJABI[1], M. P. BRANDON[2]
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Abstract: Head direction (HD) cells are one of the most abundant spatially tuned neurons in the brain. These cells are found in a series of regions starting in the brainstem and extending through the hypothalamus, thalamus, and up into the cortex areas that govern navigation and spatial memory. One area of interest is the Anterodorsal Thalamic nucleus (ADN), which contains a high concentration of HD cells (60%) and is directly downstream of the circuitry believed to initially generate the HD signal, between the dorsal tegmental nuclei and the lateral mammillary bodies. Moreover, ADN has a crucial role in the stability of the signals of other spatial cells such as the place cells and the grid cells. One major obstacle to obtaining data from this region, especially in mice, is its small size (a spherical nuclei with a 0.3mm diameter). Thus, previously reported data has rarely shown recordings of more than 10 HD cells simultaneously. Here, we show calcium imaging of more than 50 HD cells at once and during behaviour. We use a miniaturized microscope built following the guidelines of the “Miniscope” project at UCLA (miniscope.org). To reach the ADN, we implanted 0.5mm-diameter GRIN relay lenses, in mice that were injected, beforehand, with a non-specific adeno-associated virus (AAV) to express GCaMP6f, in the target region. As such, damage to the brain tissue was reduced to its minimum and recordings were stable over the course of at least two months. Calcium transients allowed us to identify HD cells by means of a simple thresholding of the fluorescence changes as well as a deconvolution-based spike inference algorithm. However, on rare occasions, GCaMP6f kinetics were not fast enough to track very quick head turns which meant that head-turn velocity had to be taken into account during the analysis. Our recordings also show a stable preferred firing direction of HD cells for more than two months. Interestingly, our data shows a possible clustering of the HD cells with regards to their preferred firing directions and a potential topographical representation of the animal’s head direction in the ADN. This preliminary finding needs to be investigated further. This technique provides the opportunity to in vivo imaging of a substantial population of HD neurons and, apart from revealing the physical arrangement of these cells, it will allow us to analyze the network dynamics of the HD system in such a way that would have been impossible otherwise.

Disclosures: Z. Ajabi: None. **M.P. Brandon:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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McGill Solvay Fellowship

Title: Dissecting the role of medial septal circuits in the hippocampal code for time

Authors: *H. YONG[1], M. P. BRANDON[2]
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Abstract: Recent work has shown that hippocampal neurons code for the time spent in the delay period on a delayed spatial alternation task. These 'time cells' have been shown to require input from the medial septum, as muscimol inactivation of the medial septum disrupted the activity of time cells and impaired memory performance. However, the exact role of the medial septum in time cell function remains unclear as muscimol-induced inactivation of the medial septum persists for the full duration of the delayed spatial alternation task. It remains possible that time cells may require information computed outside of a delay zone by other brain regions that rely on the medial septum. Further, inactivation of the medial septum with muscimol silences the activity of all septal neurons, thus it remains unknown which cell populations within the medial septum supports time cell activity. We therefore pursued an optogenetic strategy to selectively silence genetically defined cell populations within the medial septum only when the animal ran on the treadmill in a delayed alternation task. Here, we specifically tested the role of GABAergic neurons in the medial septum, which are widely believed to underlie the generation of the hippocampal theta rhythm. In this approach, we injected a cre-dependent viral vector to induce expression of Archaerhodopsin in medial septum GABAergic neurons using VGAT::Cre transgenic mice. Animals were trained to run reliably on the motorized treadmill and to alternate between the left and right arms of the maze for water reward. Animals were required to run for 20s on the treadmill between each alternation trial. Activity of time cells was recorded from CA1 region of the hippocampus with tetrodes while the medial septal GABAergic neurons were selectively silenced with a green laser (530nm) when the animal ran on the treadmill. We found that optogenetic inactivation of septal GABAergic cells cause a 70-80% reduction in theta power, similar to reduction observed with muscimol inactivation. We also found laser stimulation caused a substantial decrease in the theta rhythmicity in the spiking of individual CA1 pyramidal neurons. We are now analyzing the extent by which time cells and behavioral performance are disrupted during this optogenetic silencing of GABAergic septal cells. Next, we plan to assess the role of the remaining cell types in the medial septum including cholinergic and glutamatergic neurons. Together this data will reveal which medial septum populations are important for time cell function in the hippocampus which will help to shed light on the underlying mechanisms that code for time in the hippocampus.

Disclosures: H. Yong: None. **M.P. Brandon:** None.

Poster

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DFG - Deutsche Forschungsgemeinschaft

Title: Potential role of cholinergic medial septal inputs in coding speed and location in the entorhinal cortex

Authors: *H. DANNENBERG[1], M. E. HASSELMO[2]
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Abstract: A range of experiments show the potential role of inputs from the medial septum in coding of running speed as well as spatial location in the medial entorhinal cortex (mEC). In particular, inactivation of the medial septum causes loss of spatial periodicity of grid cells in the mEC (Brandon et al., 2011, Koenig et al., 2011), and causes the loss of spiking rhythmicity modulated by running speed that may contribute to the loss of location coding (Hinman et al., 2016). However, the cell-type specific contribution of the cholinergic neurons in the medial septum to speed and location coding in the mEC has not been addressed so far. Therefore, we use cell type-specific and stereotactically guided viral transduction of ArchT3.0 for optogenetic inactivation of medial septum cholinergic neurons during unit recording studies of the mEC in mice exploring an open-field environment. Preliminary data show that the slopes in speed tuning curves as well as the strength of speed tuning are statistically significantly reduced during laser stimulation in ArchT3.0 expressing mice, whereas no change is observed in control animals. This points to a possible role of cholinergic medial septal inputs to speed coding. In addition, our experiments reveal caveats of using laser stimulation for optogenetic inhibition of neuronal activity in the medial septum presumably due to either overheating of neuronal tissue or strong visual input due to scattered laser light. Light delivery into the medial septum in control mice causes an increase in theta frequency during movement independent of running speed. This effect is abolished by preventing light entry onto the brain indicating tissue heating as the most likely cause. In contrast to the effect of laser on field potential theta frequency, the visual input of scattered laser light alone was noted to cause significant changes in the firing rates of mEC neurons in control mice that could be reduced by better sealing of the implant. Preliminary

recording of location coding in control mice indicates that the nonspecific side effects of light delivery onto medial septum neurons do not change spatial tuning of grid cells.

Disclosures: H. Dannenberg: None. **M.E. Hasselmo:** None.

Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01 MH60013

NIMH R01 MH61492

Title: Egocentric representation of environmental boundaries in the striatum

Authors: *J. R. HINMAN[1], G. W. CHAPMAN, IV[3], M. E. HASSELMO[2]
[1]Ctr. for Systems Neurosci., [2]Psychological and Brain Sci., Boston Univ., Boston, MA; [3]Dept. of Psychology and Neurosci., Univ. of Colorodo, Boulder, CO

Abstract: Movement through space is a basic behavior, necessary for the survival of all animals. Sensory information about the world and the movements executed are both represented within an egocentric reference frame, one that is centered on the agent. An animal sees something to its left and executes movements in a given direction relative to itself based on that information, such as walking straight ahead (of itself) or turning (away from) its left. Despite the fact that sensory information and behavioral output are represented within an egocentric reference frame, an extensive allocentric, world-centered, spatial representation is maintained within the hippocampal formation that is utilized for navigating to distant goals. In order for the allocentric translation vectors generated by the hippocampal formation to be acted upon they must first be transformed into an egocentric reference frame. The hippocampal formation including the entorhinal cortex is known to mediate allocentric navigation strategies, with several allocentric spatial cell types having been identified including grid, border, head direction and place cells. An alternative, egocentric, navigation system is localized within the striatum, yet little is known about how spatial information is represented within an egocentric reference frame. We implanted rats with hyperdrives targeting the medial portion of the striatum and recorded multiple single units while they foraged in a large open field. A novel spatial cell type was identified that represents the boundaries of the environment within an egocentric reference frame that we have termed egocentric boundary cells (EBCs). Egocentric boundary cells fire when an animal is heading with a specific orientation and distance to any of the boundaries of the environment. So a given cell would fire whenever a boundary is within 10 cm on the animal's right or 20 cm to

the animal's front left for example. Across the population of EBCs the presence of boundaries at a range of angles around the animal are coded. Unlike the allocentric spatial representation in the hippocampal formation that remaps across environments, EBCs maintain a stable egocentric representation of boundary locations relative to the animal across multiple familiar, as well as novel, environments. In addition to EBCs, there are also cells that code for head direction, as well as self-motion information similar to what has been observed in parietal cortex. Overall, the medial striatum contains navigation related cells including EBCs that may be part of a larger egocentric spatial representation involved in implementing allocentric translation vectors generated by the hippocampal formation.

Disclosures: J.R. Hinman: None. **G.W. Chapman:** None. **M.E. Hasselmo:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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CREST JST JPMJCR13W1

Title: Reverse replay strengthens forward pathways to reward through Hebbian learning and short-term depression

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Abstract: In hippocampus, it has been observed that the firing sequence of place cells corresponding to a pathway experienced before is replayed in spontaneous neural activity during both sleep and awake state. Interestingly, some of sequences are replayed in reverse direction from the original experience, which is called as reverse replay (Foster and Wilson, 2006). It selectively appears when the animal is consuming reward after traversing the pathway, and is considered to be related to encoding the pathway to get reward. To generate reverse replay from the forward experience and potentiate forward memory by reverse replay in a recurrent neural network, anti-Hebbian synaptic timing-dependent plasticity (STDP) which potentiates a synapse when the postsynaptic neuron fires before the presynaptic neuron (post-to-pre) seems suitable. However, conventional STDP found in Schaffer collateral and neocortex was Hebbian (pre-to-post), the experimentally observed property of STDP in hippocampal recurrent network (CA3) was symmetric (Mishra et al., 2016), and anti-Hebbian STDP has not been experimentally observed in hippocampal excitatory synapses. Here we propose a recurrent neural network model

that overcome this inconsistency. In the presented model, we implemented the modulation of STDP effect by short-term synaptic plasticity (Froemke et al., 2006) in the recurrent network that was designed to propagate burst firing. After the generation of firing sequences, we found that recurrent synapses that transmits firing in the reverse direction were potentiated more strongly than those for the forward direction in this model. We obtained qualitatively same results in wide parameter range of short-term plasticity, and in both Hebbian and symmetric STDP. Using firing rate model, we discuss the mechanism how this phenomenon is produced by Hebbian-learning with short-term depression. We finally show that two-dimensional recurrent neural network model with Hebbian learning, short-term depression, and modulation of learning speed by reward-elicited dopamine could learn optimal pathways to the reward from any starting point on the maze.

Disclosures: **T. Haga:** None. **T. Fukai:** None.

Poster

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Title: A continuous-attractor model of head direction determination by retrosplenial 'flip cells'

Authors: *A. V. SAMSONOVICH[1,2], H. PAGE[3], K. J. JEFFERY[3]
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Abstract: Head direction (HD) cells in the rat brain cooperate to form the sense of direction. A typical HD cell fires when an animal faces in a particular direction and is silent otherwise, and HD cells in most regions maintain their relative preferred firing directions even if absolute direction is altered, such as when an orienting landmark is moved. This property is generally attributed to attractor dynamics in the underlying neuronal networks. According to the standard ring attractor model[1,2], HD cells together form a ring in some abstract space such that cells close to each other on the ring excite each other and more distant cells inhibit each other, producing a compact activity bump that can be shifted by both self-motion cues and landmarks. In apparent contradiction with this standard model is the discovery of a new type of neuron in the

dysgranular retrosplenial cortex[3], which may have a critical role in linking landmarks to the direction sense. Unlike HD cells, which encode head direction in a global reference frame, these cells rotate their directional firing by 180 degrees when an animal transitions between environmental subcompartments in which local landmark layouts are 180 degrees reversed in global space. The directional firing of these 'flip cells' can thus be disconnected from classic HD neurons. Moreover, some of these cells can exhibit a mixture of both rotation and non-rotation. Another finding challenging the standard model is that HD cells underrotate in response to landmark rotations. To reconcile these observations with the standard model we assume that there is not one, but two or more weakly inter-connected attractor rings. Some rings are strongly bound to particular landmarks, while others are mostly driven by background cues, which include the current heading estimation sustained by self-motion cues. To validate the concept we performed simulations of a simple two-ring continuous-attractor neural network model, using non-spiking linear-threshold units with a Gaussian distribution of excitatory connections and global inhibition that stabilizes the total number of active units. Under a choice of parameters consistent with published experimental data, the model easily reproduces all qualitative aspects of observed dynamics, including discordant HD representations and the flip cell phenomenon. It may explain how retrosplenial cortex contributes to the landmark control of the direction sense.
1. Skaggs WE, Knierim JJ, Kudrimoti HS, McNaughton BL.(1995) Adv Neural Inf Process Syst. 7:173-80. 2. Zhang K. (1996) J Neurosci. 1996 Mar 15;16(6):2112-26. 3. Jacob PY, Casali G, Spieser L, Page H, Overington D, Jeffery K. (2017) Nat Neurosci. 20(2):173-175.

Disclosures: **A.V. Samsonovich:** None. **H. Page:** None. **K.J. Jeffery:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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ANR BLANC 2008 BRAIN GPS

MIRG-CT-21939

CNRS PEPII

Title: Two star mazes, but a single representation of space in the monkey hippocampus

Authors: P. BARADUC[1], S. PINEDE[2], A. PLANTÉ[2], *J.-R. DUHAMEL[2], S. WIRTH[2]
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Abstract: How does the brain code similarities between different experiences while also discriminating their specificity? Studies of spatial memory have provided ample evidence that different episodes are coded by distinct patterns of cell activity. In the rodent foraging for food, hippocampal cells signal the animal's location through a place field. These place fields change when elements of the environment are altered, and a global remapping occurs when the animal is placed in different enclosures. Here we asked how hippocampal cells in the monkey code two virtual reality environments bearing a similarity of structure but different visual landmarks. We previously showed that the primate hippocampus codes space during wayfinding in more complex ways than simple place-coding, and includes task-related information, among which the progression towards the goal (Wirth et al., 2017, *PLoS Biol* 15(2): e2001045). We now compare the activity maps obtained when the animal searches for a hidden reward in a familiar, well-known star maze vs. a novel maze of same shape, but differing in the visible landmarks. We showed that while 35% coded only one environment, 29% of cells coded both environments. In 71% of the latter cells, activity maps showed a higher cross-correlation than expected by chance between the familiar and the novel maze. Thus, while physical landmarks changed, these cells maintained a goal-centered and task-related representation of space. This abstract representation progressively formed as a function of learning, as the cross-correlation steadily increased across learning epochs. Crucially, this progression was apparent when decoding cell activity in task-related state space or goal-centered physical space, but not as a function of either view direction or point of gaze. To summarize, some cells abstracted from the physical details of the maps and only coded high-level, goal- and task-related information in schema-like representation; the other maze-selective cells could concurrently represent the uniqueness of the perceptual and/or episodic experience.

Disclosures: P. Baraduc: None. **S. Pinede:** None. **A. Planté:** None. **J. Duhamel:** None. **S. Wirth:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: Wellcome/DBT India Alliance grant IA/S/13/2/501024

Title: Cheap, scalable camera system for tracking rat behavior in large spaces

Authors: R. SAXENA, D. JAIN, I. R. JAKHALEKAR, W. BARDE, A. BISHNOI, *S. S. DESHMUKH
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Abstract: The hippocampal spatial map is thought to be a cognitive construct, representing the abstract notion of space rather than sensory stimuli. Barring a few heroic efforts, studies have remained limited to environments smaller than $1m^2$, thanks to the limits imposed by cables running from the animal to the recording system. Wireless recording enables us to record in larger and more complex environments, approaching the scale and complexity of natural environments. Most commercial neurophysiology systems, however, use one camera (or at most two) to track the animals, further limiting the experiments to small spaces.
We have developed a novel tracking system comprising 8 overhead Raspberry Pi cameras, which is capable of tracking animal position in a large environment. The video tracking system is temporally synchronized with neural data recorded on a Neuralynx Cheetah data acquisition system using TTL pulses. The Pi cameras have a jitter of ±0.025ms in the inter-frame intervals as compared to the ±8ms jitter in the inter-frame interval of the Neuralynx camera system. This reduction in jitter allows a more accurate estimation of the animal's position at any given time, by reducing the misalignment between tracking and neural data streams. This system is scalable and hence can be used for environments larger than the one used in the present study. Also, the system is adaptable for use with complex environments with multiple occlusions. Use of cheap, off-the-shelf components makes this system significantly cheaper than off-the-shelf multi-camera video tracking systems. Furthermore, it is temporally more accurate compared to commercially available neurophysiology systems. We will present data showing neural correlates of space in hippocampus and related areas recorded using this system and an explicit comparison of recordings from the Pi camera system with a commercial system.

Disclosures: R. Saxena: None. **D. Jain:** None. **I.R. Jakhalekar:** None. **W. Barde:** None. **A. Bishnoi:** None. **S.S. Deshmukh:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: ERC #639272

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MSCA IF #753608

Title: *In vivo* two-photon imaging of cortical head direction cells during passive rotation

Authors: *A. R. CHAMBERS[1], E. HENNESTAD[1], R. LANTON[1], W. TANG[2], K. VERVAEKE[1]

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Abstract: Accurate spatial navigation depends upon the brain's capacity to generate an internal, continuous representation of head direction (HD). Neurons that are selectively active when the animal is facing a specific direction, so-called HD cells, form the neural basis for this representation, and can be found in multiple brain areas, including the retrosplenial cortex (RSC). The RSC boasts reciprocal connections with several key brain regions for memory and navigation, such as the hippocampal formation and anterior thalamic nuclei, however its microcircuit architecture and exact role in navigation remain unclear. In addition, it is unknown whether RSC HD cells transform incoming directional information to generate HD tuning, or whether they simply inherit this tuning from upstream regions. Cellular studies of HD representation are generally performed with extracellular recordings, which are limited in their ability to reveal the spatial organization and cellular identity of HD-tuned neurons, and lack the ability to densely sample the whole population. Extracellular recordings may also display a bias toward active neurons, thereby complicating an accurate estimate of HD tuning prevalence. For these reasons, a paradigm for chronic, *in vivo* two-photon imaging of HD cells is of great interest to the field. HD cell tuning, however, depends on vestibular stimulation and is anchored to visual cues. Therefore, we developed a setup that allows rotating awake and head-fixed mice under the microscope objective, while keeping visual cues on the surrounding arena stable. Using a genetically encoded Ca2+ indicator (GCaMP6f) to measure neural activity, we found that passive rotation is sufficient to elicit tuned responses from HD cells. We are currently characterizing the properties of HD neurons in light and dark conditions, and in response to visual rotations, as well as mapping the spatial distribution of these cells across cortical layers and subdivisions of the RSC.

Disclosures: A.R. Chambers: None. **E. Hennestad:** None. **R. Lanton:** None. **W. Tang:** None. **K. Vervaeke:** None.

Poster

710. Hippocampal Circuits Involved in Learning and Memory

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Support: Israel Science Foundation FIRST program Grant 281/15

Helmsley Charitable Trust through the Agricultural, Biological and Cognitive Robotics Initiative of Ben-Gurion University of the Negev

Title: Search for allocentric navigation encoding in the goldfish brain

Authors: E. VINEPINSKY, *O. DONCHIN, R. SEGEV
Ben Gurion Univ., Be'er Sheva, Israel

Abstract: The ability to navigate in the world is extremely important to almost all animals. In mammals, the neural navigation system is believed to be based on place cells and grid cells which are found in hippocampus and the entorhinal cortex. However, it remains an open question whether similar navigation system exists in other animal classes. To address this fundamental issue, we use the goldfish as a model animal since it possesses a defined neuroanatomical region associated with allocentric navigation. Using a wireless recording system, we measured the activity of single cells in the lateral pallium while it swims in a quasi-1D aquarium. We found two unique cell types: velocity cells and speed cells. Velocity cells encode swimming direction and speed and therefore have allocentric properties, while speed cells encode only the speed independent of direction. We have also found some evidence of border cells, i.e. cells which are active when the fish is near the boundary of the environment. Our study sheds light on how the fish brain encodes spatial information and how the mechanisms of a neural navigation system are preserved across evolution.

Disclosures: E. Vinepinsky: None. **O. Donchin:** None. **R. Segev:** None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

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Program#/Poster#: 711.01/UU5

Topic: H.01. Animal Cognition and Behavior

Title: L-Thyroxine normalizes hypothyriodism-induced suppression of CaMKII pathway during hippocampus-dependent learning and memory processes

Authors: K. H. ALZOUBI[1], *K. A. ALKADHI[2]
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Abstract: Calcium/calmodulin protein kinase II (CaMKII) is a crucial molecule for hippocampus-dependent learning and memory. Activation of CaMKII is triggered by an increase in intracellular calcium concentration, which activates PKCγ. This frees calmodulin, which activates CaMKII forming phosphorylated (P-) CaMKII. Recently, we have shown that hypothyroidism impairs hippocampus-dependent learning and memory in adult rats. L-thyroxine treatment, on the other hand, alleviates cognitive deficits during hypothyroidism. In this study, we investigated the interactive effect of L-thyroxine and hypothyroidism on the CaMKII pathway during learning and memory processes. To locate a hidden (2cm under water) platform, each rat was trained in the radial arm water maze (RAWM) for 8 consecutive learning trials. Thirty minutes later, a memory test was done, and immediately after that hippocampi were

dissected out, and CA1 areas were removed and processed for determination of P-CaMKII, total CaMKII, PKCγ and calmodulin protein levels. Results from RAWM-trained rats were compared with those from age-matched controls, hypothyroid and L-thyroxine treated/hypothyroid animals that underwent the same number and duration of swimming trials, but to locate a clearly visible (2cm above water) platform in an open (non-RAWM) swim field.
Western blot analysis revealed a significant increase in P-CaMKII in the CA1 region of the hippocampus in RAWM-trained control and L-thyroxine treated/hypothyroid groups, but not in the hypothyroid group compared to non-RAWM corresponding groups.
However, no significant increase was found in the levels of total CaMKII, calmodulin, and PKCγ in CA1 area of the hippocampus of all RAWM trained rats compared to non-RAWM corresponding groups. Therefore, our study shows that chronic L-thyroxine treatment normalizes hypothyroidism-induced suppression of P-CaMKII levels during hippocampus dependent learning and memory.

Disclosures: K.H. Alzoubi: None. **K.A. Alkadhi:** None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

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Topic: H.01. Animal Cognition and Behavior

Support: NHMRC #1126929

Brain Sciences UNSW Collaborative Grant

Title: Oral minocycline hydrochloride prevents hippocampal-dependent cognitive impairment associated with cafeteria diet both before and after the onset of obesity

Authors: *S.-J. LEIGH[1], R. F. WESTBROOK[2], M. J. MORRIS[3]
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Abstract: Background: While a large body of literature indicates that obesogenic diets are associated with cognitive impairment in both human and animal models, the underlying mechanisms remain controversial. A key mechanism proposed to drive these cognitive changes is increased inflammatory signalling associated with obesity. The anti-inflammatory minocycline hydrochloride (MH) has been routinely used to depress microglial activity as it easily crosses the blood brain barrier. We used a rodent model to test the hypothesis that blocking inflammatory signalling in the periphery and brain with MH would alleviate cafeteria-diet-induced cognitive deficits. **Methods:** Rats were pre-exposed to vehicle (syrup) or MH (40mg/kg/day) for three

days before half were switched from regular chow to a cafeteria diet, consisting of regular chow, various cakes, biscuits, savoury foods and 10% sucrose. Memory was tested using novel object and place recognition tasks (NOR and NPR respectively) at two, four and six weeks of diet; EchoMRI performed at four and six weeks determined body composition. Two to three days following final behavioural testing and EchoMRI, rats were euthanised and brain, blood and peripheral tissues collected. **Results:** Rats fed cafeteria diet and vehicle were impaired on the hippocampal-dependent NPR throughout the experiment, and a mixed three-way ANOVA revealed no effect of time on NPR performance. Average place task exploration ratios showed a significant interaction effect between diet and drug; while MH administration spared NPR performance in cafeteria-fed rats (similar exploration ratios to rats fed chow and vehicle), chow rats treated with MH performed worse than those treated with vehicle. For both chow and cafeteria rats administered vehicle, final body weight was negatively associated with average NPR exploration ratio ($r=-.60$, $p<.001$) with heavier rats performing worse on the hippocampal-dependent task. This association was not observed in MH-treated rats: final body weight was not associated with performance on NPR. MH administration did not alter 24-hour energy intake in either diet group. **Conclusions:** Cafeteria diet produced persistent deficits in NPR and this deficit was prevented by ingestion of the anti-inflammatory drug MH, indicating that these cognitive impairments may be associated with increased inflammatory signalling. However, since MH also has antibiotic activity, further investigation into the role of the gut-brain axis in diet-induced cognitive impairments is underway.

Disclosures: S. Leigh: None. **R.F. Westbrook:** None. **M.J. Morris:** None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

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Support: Lebanese American University SRDC grants

Title: Lactate mediates the effects of exercise on learning and memory through Sirt-dependent BDNF induction

Authors: *S. SLEIMAN, L. EL-HAYEK, V. ZIBARA, R. ABI ASSAAD, N. EMMANUAL, N. KARNIB, R. EL-GHANDOUR
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Abstract: Exercise induces beneficial responses in the brain, which is accompanied by an increase in BDNF, a growth factor associated with cognitive improvement and the alleviation of depression and anxiety. However, the exact mechanisms by which physical exercise produces an

induction in brain *Bdnf* gene expression are not completely understood. Here, we report that an endogenous molecule released after exercise is capable of inducing *Bdnf* promoters. The metabolite lactate, which is increased after prolonged exercise in the blood, induces *Bdnf* expression and Trkb signalling in the hippocampus. Indeed, we find that lactate-dependent increases in hippocampal BDNF are associated with improved spacial learning and memory retention and rescue of chronic social defeat. We have discovered that the action of lactate is dependent on Sirt induction and activation potentially by affecting the activity of the transcriptional coactivator PGC1α. These results reveal an endogenous mechanism to explain how physical exercise leads to the induction of BDNF and identify novel targets that allow us to harness the therapeutic potential of exercise.

Disclosures: S. Sleiman: None. **L. El-Hayek:** None. **V. Zibara:** None. **R. Abi Assaad:** None. **N. Emmanual:** None. **N. Karnib:** None. **R. El-Ghandour:** None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 711.04/UU8

Topic: H.01. Animal Cognition and Behavior

Support: NHMRC

Title: Obesogenic diets affect cognition in rats through gut microbiome and associated chnages in brain neuroplasticity and inflammation

Authors: *M. J. MORRIS, J. BEILHARZ, J. MANIAM, N. KAAKOUSH
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Abstract: A range of studies in animals and humans have demonstrated that exposure to diets rich in either fat and sugar, or sugar alone, can have detrimental effects on cognition. The hippocampus appears particularly sensitive to dietary insult, specifically hippocampal-dependent place recognition memory. People who report greater consumption of fats and sugars showed more marked loss of hippocampal volume. While the Western diet is known to have detrimental effects on cognition and the gut microbiota, few studies have investigated how these may be related. Our lab examines the relationship between diet-related changes in gut microbiota, hippocampal gene expression and behavioural deficits using Sprague Dawley rats. Exposure to a cafeteria diet rich in fat and simple sugars impairs hippocampal dependent spatial learning within 1 week, prior to significant weight changes. Purified diets that were enriched in saturated fats or simple sugars had a similar impact, with changes in microbiota composition in the absence of changes in body weight. We next examined whether probiotic administration could prevent diet-induced memory deficits. Rats were pre-exposed to vehicle, low or high doses of the probiotic

VSL#3 daily for 2 weeks before half were switched from chow to a cafeteria diet for 25 days; VSL#3 treatment continued throughout. Fecal DNA extraction was performed by PowerFecal® DNA Isolation Kit. Cafeteria fed rats were heavier with greater fat mass than those consuming chow, and the probiotic had no impact on these measures. High dose VSL#3 prevented cafeteria diet-induced memory deficits on the hippocampal-dependent place task, but the probiotic led to deficits on the perirhinal-dependent object task, irrespective of diet or probiotic dose. No differences were observed in anxiety-like behaviour on the elevated plus maze. Gut microbial diversity was dramatically decreased by cafeteria diet and here, VSL#3 was able to increase the abundance of some taxa contained in the probiotic such as *Streptococcus* and *Lactobacillus*. In the hippocampus, the cafeteria diet increased expression of many genes related to neuroplasticity and serotonin receptor (5HT) 1A, which was normalised in cafeteria rats on high dose VSL#3. Neuroplasticity genes in the perirhinal cortex were also affected by diet. Object memory performance was correlated with perirhinal 5HT2C expression. These results show that probiotics can be beneficial in situations of gut dysbiosis where memory deficits are evident but may be detrimental in healthy subjects.

Disclosures: **M.J. Morris:** None. **J. Beilharz:** None. **J. Maniam:** None. **N. Kaakoush:** None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 711.05/UU9

Topic: H.01. Animal Cognition and Behavior

Title: Polyphenol-enriched green tea extract restores depressive symptoms and hippocampal synaptic plasticity in ovariectomized rat

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Abstract: The depressive disorder is a common but serious disorder that causes severe symptoms that affect feel, think, and handle daily activities. The depressive disorder is more abundant in post-menopausal woman because it is commonly caused by the loss of ovarian follicular activity. Many research showed that synaptic strength changes by stress in cortex, hippocampus, and amygdala are implicated in depressive symptoms, which lead to abnormality of cognition and memory impairment. Recent studies showed that green tea has brain tranquilizing effect, and intake of green tea decreased the stress response in human. In addition, tea polyphenols of green tea has been known to be the main effector for these effects. In this study, therefore, we hypothesized that intake of green tea polyphenol restores hippocampal synaptic dysfunction which induces cognitive deficits in post-menopausal state. To investigate this hypothesis, we tested the effect of polyphenol-enriched green tea extract (PeGTE) on the

impairment of synaptic function at the CA1-Schaffer's Collateral (SC) pathway in hippocampus in depressed, ovariectomized (D-OVX) female rat. It was found that the synaptic strength efficiency at SC pathway in D-OVX rat was significantly suppressed compared to Sham-operated rat. This synaptic impairment was mainly due to serious loss of silent synapses formation, which led to impairment of functional connectivity and LTP capability at the hippocampal SC pathway in D-OVX rat. Surprisingly, these impairments of the hippocampal synaptic function in D-OVX rats were significantly ameliorated by PeGTE treatment. Taken together, these data showed that the synaptic function in hippocampus was significantly deteriorated by depression induction in OVX female rats compared to sham-operated groups. In addition, PeGTE treatment significantly improves the synaptic dysfunctions in D-OVX rats. From these findings, we suggest the possibility that green tea polyphenol may be therapeutic strategy to increase resilience and reduce the cognitive deficits in women who are susceptible to stress and memory impairment by menopause.

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

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 711.06/UU10

Topic: H.01. Animal Cognition and Behavior

Support: MRC Case Studentship

Title: Impaired hippocampal gamma-frequency oscillations and mitochondrial dysfunction in a mouse model of alpha-synucleinopathy

Authors: *F. E. RANDALL[1], C. TWEEDY[2], E. ROBSON[2], A. REEVE[2], G. J. CLOWRY[2], E. OLKHOVA[2], J.-P. TAYLOR[2], P. J. ATKINSON[3], F. E. N. LEBEAU[2]
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Abstract: The misfolding and aggregation of the protein alpha-synuclein is a key pathological feature of the alpha-synucleinopathies, a group of diseases which includes Lewy body dementia and Parkinson's disease. A common symptom of alpha-synucleinopathy is cognitive dysfunction and dementia. Impairment in hippocampal gamma-frequency oscillations may underlie some of the cognitive deficits associated with alpha-synucleinopathy. The Thy-1 A30P mouse model overexpresses human mutant alpha-synuclein, with mice developing hippocampal spatial memory impairment by 12 months of age (Freichel et al. 2007). The aim of this study is to explore age-related hippocampal network changes in 2-3 month and 10-16 month old A30P mice to assess the effect of overexpression of mutant alpha-synuclein on cortical network oscillations

in vitro. Following sucrose perfusion of anaesthetised mice, 450µm transverse hippocampal slices were prepared. Persistent gamma-frequency oscillations can be evoked by the cholinergic agonist carbachol, with oscillation power building over 2-4 hours before reaching stability. Extracellular field recordings were carried out in the CA3 region of A30P and wild-type mice. Mitochondrial function is crucial for the generation of GFO's (Whittaker et al. 2011) and was assessed by COX/SDH double labelling histochemistry on a separate cohort of snap frozen brains. Compared to wild-type mice, A30P mice display an impairment in the build-up and stabilisation of gamma-frequency oscillations at 10-16 months (n=6, p=0.035), but not at 2-3 months (n=10, p=0.838). Mitochondrial function was also found to be impaired in 10-16 month A30P mice compared to 2-3 month A30P mice (n=5 mice each, p=0.04). Mitochondrial dysfunction may be a cause or consequence of gamma-frequency oscillation impairment within the CA3 region of the hippocampus. These changes have implications for the pathogenesis and treatment of alpha-synucleinopathies and will be explored further.

Disclosures: **F.E. Randall:** A. Employment/Salary (full or part-time):; Eisai Inc. **C. Tweedy:** None. **E. Robson:** None. **A. Reeve:** None. **G.J. Clowry:** None. **E. Olkhova:** None. **J. Taylor:** None. **P.J. Atkinson:** A. Employment/Salary (full or part-time):; Eisai Ltd. **F.E.N. LeBeau:** None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 711.07/UU11

Topic: H.01. Animal Cognition and Behavior

Support: MRC Case Studentship

Title: Early hippocampal network hyperexcitability in a mouse model of alpha-synucleinopathy

Authors: ***C. TWEEDY**[1], J. CURRY[1], G. J. CLOWRY[1], A. REEVE[1], E. OLKHOVA[1], J.-P. TAYLOR[1], F. E. RANDALL[2], P. J. ATKINSON[3], F. E. N. LEBEAU[1]
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Abstract: A balance of excitation and inhibition within the hippocampal network is crucial for the timing and synchrony of network rhythms critical to learning and memory processes. Sharp waves are believed to be involved in memory consolidation and in an acute brain slice preparation of isolated hippocampus (450µm thick), spontaneous sharp waves can be observed in CA3. Changes in sharp wave properties could indicate a network imbalance and therefore underpin the impairment of hippocampal memory processes in diseases such as dementia. The second most common cause of neurodegenerative dementia is alpha-synucleinopathy (including

Lewy body dementia and Parkinson's disease). A mouse model of alpha-synucleinopathy was used to explore changes in the hippocampal excitatory-inhibitory network and investigate its relation to memory deficits. Thy-1 A30P mice overexpress human mutant alpha-synuclein throughout the brain, and develop cognitive dysfunction by 12 months of age (Freichel et al. 2007). Following transcardial perfusion with a high sucrose solution, spontaneous sharp waves were recorded in A30P and wild-type control mouse slices at 2-3 and 10-12 months of age. Sharp waves were found to be of significantly greater amplitude within the 2-3 month A30P hippocampus compared to all other groups (n=7-9 mice per group, 14-21 slices each, p=0.011). Network dysfunction was further explored with exposure to 150nM kainate. At 2-3 months all wild-type control slices exhibited persistent gamma-frequency oscillations with kainate (n=8 slices). However, in 2-3 month A30P mice, 56% of slices also exhibited interictal discharges (n=11 slices). Ageing led to a small increase in the incidence of interictal activity in 10-12 month wild-type mice (9% of slices, n=22). Interestingly, there was a reduced incidence of interictal activity in 10-12 month A30P mice (13% of slices, n=16 slices), suggesting that excitability returned to similar levels as wild-type with ageing. This suggests an early hyperexcitable hippocampal network, becoming less excitable with ageing in A30P mice as cognitive dysfunction becomes apparent. Hyperexcitability may therefore contribute to, or be a predictor of, later wider network dysfunction and therefore act as an early biomarker or potential point of intervention.

Disclosures: C. Tweedy: None. **J. Curry:** None. **G.J. Clowry:** None. **A. Reeve:** None. **E. Olkhova:** None. **J. Taylor:** None. **F.E. Randall:** A. Employment/Salary (full or part-time):; Eisai Inc. **P.J. Atkinson:** A. Employment/Salary (full or part-time):; Eisai Ltd.. **F.E.N. LeBeau:** None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 711.08/UU12

Topic: H.01. Animal Cognition and Behavior

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Title: MPH reestablish the behavior and hippocampal plasticity in a mouse model of ADHD induced by prenatal nicotine exposure

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Abstract: Attention deficit and hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder of childhood and is characterized mainly by hyperactivity, impulsivity, impaired attention and learning deficit. Methylphenidate (MPH) is the most commonly medication used to treat ADHD, however the molecular mechanisms involved in this process are still unknown . In this study we examined the effects of MPH on hipocampal synaptic plasticity in a model of ADHD induced by prenatal nicotine exposure (PNE). Using electrophysiological approaches and Western blot analysis we investigated TBS-dependent LTP in CA3-CA1 synapses of hippocampus and the insertion of AMPA receptors in the postsynaptic membrane. The characterization of the ADHD was assessed measured the locomotor activity using Open Field Test (OFT), working memory with Y-Maze test and attention with an Object Base Attention test (OBA). LTP was induced by applying theta burst stimulation (TBS, 5 trains, 100 Hz) in hippocampal slices (300 µM) obtained from Control and PNE mice (3-4 weeks old). Our results show that PNE mice exhibit the symptoms of ADHD and that oral administration of therapeutic doses of MPH (1 mg/kg) decreases these behavior significantly. PNE mice showed a significant reduction of LTP compared to controls: from 152.9±0.68% to 127.0±0.81% (n=10,10; *p<0.05). This effect was reverted after of oral administration of 1mg/Kg MPH to levels similar to the observed in control mice: from 127.0±0.81% (n=10,10) to 151.9±1.34 (n=4,4; *p<0.05). In or der to evaluated the molecular mechanism involved in this process we measured the change in the phosphorylation levels of GluA1 subunits of AMPA receptors. Our experimental approach was to collect CA1 areas from hippocampal slices used in electrophysiological experiments for Western blot analysis. Consistent with our electrophysiological results, a significant decrease in phosphorylation ratio for GLUA1-Ser831 was found in PNE mice that showed reduced LTP versus controls mice (PNE: 0.67±0.05, n=5; Controls: 0.93±0.01, n=4; **p<0.01). No significant change in the phosphorylation ratio of GLUA1-Ser845 was observed (PNE: 0.55 ±0.9, n=5, control: 0.6 ±0.12 n=4; p > 0.05). Taken together, our results suggested that oral administration of MPH reestablished the low LTP observed in PNE mice, we hypothesized that this effect is possibly by mobilization of AMPA receptors to the postsynaptic membrane in the CA3-CA1 synapses.

Disclosures: D. Contreras Pacheco: None. **C.A. Carvallo:** None. **R. Piña:** None. **G. Ugarte:** None. **M. Zeise:** None. **R.A. Delgado:** None. **J. Klagges:** None. **D. Morales:** None. **M. Albornoz:** None. **C.A. Rozas:** None. **B.E. Morales:** None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 711.09/UU13

Topic: H.01. Animal Cognition and Behavior

Title: Differential cFos expression after Morris Water Maze exposure in cortical malformation model

Authors: *W. J. CURRY, III
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Abstract: Malformations of cortical development (MCDs) are disruptions of neuronal migration and development that often accompany childhood epilepsy, with 40% of children with refractory epilepsy exhibiting these malformations. MCDs in children with epilepsy are also associated with cognitive impairment and developmental delay. When injected into pregnant dams at embryonic day (E17), methylazoxymethanol acetate (MAM), a DNA alkylating agent, produces offspring with cortical dysplasia that mirrors the phenomenon in humans. Previous work indicates that MAM animals indeed have disorganized hippocampi, hyperexcitability leading to increased seizure susceptibility and perform worse on hippocampus-dependent tests of spatial navigation such as the Morris water maze and place avoidance tasks. Our current work seeks to understand the degree to which neurons directly affected by MAM versus those neighboring neurons that developed in the context of the MAM abnormality are involved in the aberrant network activation that leads to hyperexcitablility. We tested this by performing immunohistochemical analysis of brain sections from 4 cohorts of rats: 1) Control, 2) Control + Morris Water Maze exposure, 3) MAM, and 4) MAM + Morris Water Maze exposure. Levels of hippocampal network activation were measured by levels of c-Fos, a marker of neuronal activation and MAM-affected neurons were labeled with co-administered BrdU. Interestingly, analysis revealed that after water maze exposure, control animals showed greater levels of cFos activation, whereas there was no difference in cFos expression between MAM and MAM + Water Maze groups. Future studies are ongoing to confirm these findings and examine the relationship between BrdU/c-Fos positive and BrdU/c-Fos negative populations. Additional studies are being conducted in order to determine the relationship between putative network abnormalities and cognitive impairment.

Disclosures: W.J. Curry: None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 711.10/UU14

Topic: H.01. Animal Cognition and Behavior

Title: Characterizing the effect of asynchronous distributed microelectrode stimulation on spatial memory

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Abstract: Introduction: There is a great need of a therapeutic method for treating epileptic patients that is characterized by a high success rate in seizure frequency reduction and minimal side effects. Asynchronous Distributed Microelectrode Stimulation (ADMETS) has been shown to significantly reduce seizure frequency in the tetanus toxin rat model of epilepsy. However, critical to developing novel neural modulation therapies will be rigorous assessment of how they impact behavior. In this project, we aim to characterize the effects of ADMETS on the hippocampal circuity and its manifestation in terms of spatial memory.
Methods: A rat was implanted in the CA1 and CA3 regions of the hippocampus with a 16-channel microelectrode array, with alternating 8 stimulating and 8 recording channels. The ADMETS stimulation parameters that were studied were the standard 4 Hz, 2V stimulation as well as a 7 Hz, 4V stimulation. The spatial object recognition task utilizes the innate behavior of rats to explore novelty to assess spatial memory. The rat was allowed to explore 3 objects in an open-field box for 3 minutes. The rat is then removed from the arena, the objects are cleaned to remove olfactory cues, and 2 of the objects switch positions. After a short delay, the rat is re-introduced to the open-field box. Normal memory function is characterized by an increase of interaction time on the objects that switched positions. The task was assessed for the pre-stimulation, stimulation/sham-stimulation, and post-stimulation periods.
Results: Both ADMETS stimulation parameters showed a significant decrease in memory during stimulation as well as during the post-stimulation period when compared to the pre-stimulation trial. The average discrimination score for the stimulation and sham-stimulation trials for the standard ADMETS was 0.59 and 0.28 respectively (p-value=<0.001), and 0.44 and -0.19 for the 7 Hz, 4 V stimulation(p-value=0.01). A more positive score is indicative of better memory.
Discussion: The results indicate that for both ADMETS stimulation parameters, functionality of the hippocampus was affected detrimentally during stimulation as well as 10 minutes after stimulation. Comparing the stimulation and sham-stimulation trials for both experiments, we calculated an effect size of 0.97 for the 4Hz, 2V stimulation and an effect size of 1.34 for the 7

Hz, 4 V stimulation. This suggests there is a dynamic relationship between seizure frequency and spatial memory for different stimulation parameters that are utilized.
Conclusion: Optimization of both stimulation paramaters and behavioral biomarkers is critical in the development of novel neuromodulation therapies.

Disclosures: O. Ashmaig: None. **M.J. Connolly:** None. **R.E. Gross:** None. **B. Mahmoudi:** None.

Poster

711. Learning and Memory: Hippocampal Circuits in Disease Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 711.11/UU15

Topic: H.01. Animal Cognition and Behavior

Title: The effect of multiple levels of chronic zinc supplementation on b6 mice

Authors: *T. DIMOPOULOS, M. L. SMITH, W. R. KOCHEN, N. COSCHIGANO, J. M. FLINN
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Abstract: Zinc is an essential biometal located in multiple areas of the brain, predominantly in Zinc-enriched Neurons (ZENs) in the hippocampus. The role of zinc homeostasis in the brain has been implicated in many disorders. Zinc has been shown to bind to tau and exacerbate Tauopathy, having a detrimental effect in both in vitro and in vivo studies. On the other hand, elevated Zinc in a patient's urine following a Traumatic Brain Injury directly correlated to the injury severity as well as depression levels after injury pointing towards the importance of zinc in the brain. Both of these examples point to the critical role of zinc homeostasis in the brain; however, no study has looked at the effect of multiple levels of chronic zinc exposure to determine the potential beneficial or detriment study examined the effect of zinc exposure for 6 months on mice consuming either lab water, or water supplemented with 10, 20, or 40 parts per million zinc supplemented water. These mice were then tested on nesting activity, fear conditioning, and the Morris water maze. Histochemistry including Zinpyr staining was also performed to assess the role and location of zinc in the brain.

Disclosures: T. Dimopoulos: None. **M.L. Smith:** None. **W.R. Kochen:** None. **N. Coschigano:** None. **J.M. Flinn:** None.

Poster

712. Learning and Memory: Aging and Behavior

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 712.01/UU16

Topic: H.01. Animal Cognition and Behavior

Support: U54 GM104942

Title: Cognitive impacts of recurring inflammatory/infection-like experiences during aging

Authors: *E. B. ENGLER-CHIURAZZI[1,2,3], J. M. POVROZNIK[1,2,3], A. E. RUSSELL[1,2,3], K. N. PORTER[3,4], D. WANG[1,2], B. G. SCHREURS[1,2], J. W. SIMPKINS[1,2,3]
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Abstract: Infections are common occurrences in life. In addition to inducing sickness behaviors, infections also acutely impact cognition. While the immediate consequences of infection are known, the long-term cognitive consequences of repeated intermittent infections are not well-studied; some evidence suggests that higher lifetime infection burden is associated with greater cognitive decline. Here, we investigated recurring inflammatory/infection-like experiences, health outcomes, and cognitive performance in aging mice, hypothesizing that repeated immune activation could explain, at least in part, age-related cognitive decline. C57BL/6 male mice (10 months) received an intraperitoneal injection of vehicle or LPS every 14 days for 2.5 months. For each injection, the dose of LPS was increased according to the following: 0.4 (Injection 1), 0.8 (Injection 2), 1.6 (Injection 3), 3.2 (Injection 4), and 6.4 (Injection 5) mg/kg. We evaluated sickness behaviors using a 20-point scale at 4 hours, and 14 days, post-injection. Following the final injection/recovery period, animals were cognitively characterized. A subset of the cognitively tested mice as well as groups of behaviorally naïve animals subjected to the same treatment regimen as described above were assessed for long-term potentiation. We predicted that 1) following each exposure, LPS treatment would induce a moderate sickness response from which animals would make a full or nearly full recovery, and 2) this repeated inflammatory/infection-like experience would detrimentally impact cognitive ability and reduce long-term potentiation. Results indicated that at each injection, LPS treatment induced moderate sickness behavior within 4 hours of exposure; 2 weeks post-injection, LPS-treated animals exhibited health/sickness scores similar to Vehicle-treated controls. For behavioral outcomes, LPS-treated mice showed inferior learning on tests of cognitive performance (i.e. passive avoidance). As well, field potential recordings revealed that LPS administration produced a pronounced reduction in LTP expression in mice that had been behaviorally characterized or

who were behaviorally naïve. Thus, recurring infection-like experiences via repeated LPS injections during mid-life transiently produced sickness behaviors but induced long-lasting detrimental cognitive impacts and modulated synaptic plasticity of the hippocampal CA1 neurons that may mediate the observed functional changes. These findings indicate that frequency of immune activation may influence the trajectory of age-related cognitive decline and could be a therapeutic target to facilitate 'graceful aging'.

Disclosures: E.B. Engler-Chiurazzi: None. **J.M. Povroznik:** None. **A.E. Russell:** None. **K.N. Porter:** None. **D. Wang:** None. **B.G. Schreurs:** None. **J.W. Simpkins:** None.

Poster

712. Learning and Memory: Aging and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 712.02/UU17

Topic: H.01. Animal Cognition and Behavior

Title: Learning and memory enhancing efficacy of Withania somenifera in aged mice

Authors: *M. LATA[1], P. SRIVASTAV, 302021[2]
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Abstract: In learning activation of neuron occur in specific area whereas memory is a storage form of learned information and retain them over period of time. Poor memory, lower retention are common problem in old age. In Ayurveda ,Madhya rasayna, are said to prevent aging, have rejuvenate property and supposed to have influence on brain function. *Withania somenifera* is one of them.
Aim: The aim of this study was to evaluate the effect of *Withania somenifera* on behavior changes (learning and memory)of aged mice when administrated the extract for various duration in varying doses i.e., 100mg/kg and 200mg/kg bw.
Method: We divided the animals of 8months , 10months and12months old mice into2-,4-week pre treated and control(n=6 for each group). After the treatment period, the mice along with age matched normal and control mice were subjected to spatial learning(radial arm maze) and passive avoidance tests.
Result: The data was compared with those of age matched control mice. *Withania somenifera* attenuated GPx activity and inhibit LPO in dose dependent manner. The result of radial maze tests in treated group showed significant improvement in learning behavior ($p<0.001$). whereas retention test, treated group spent less time in the smaller compartment but not significantly significant as compared to respective control.
Conclusion: Results clearly indicate the oral administration of *Withania somenifera* extract improved learning and memory in aged mice.

Disclosures: **M. Lata:** None. **P. Srivastav:** None.

Poster

712. Learning and Memory: Aging and Behavior

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Northwestern University: Nicholson Fellowship

Title: Conditioning-induced modulation of theta activity in dentate gyrus, entorhinal cortex and perirhinal cortex

Authors: *E. E. SUTER[1], C. WEISS[2], J. F. DISTERHOFT[3]
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Abstract: Theta oscillations are important in acquisition and retention of hippocampal-dependent tasks, and stimulus-specific theta modulations in CA1 remain strong throughout acquisition and consolidated performance of trace eyeblink conditioning. However, dentate gyrus theta rhythm is less well explored and it is unclear whether hippocampal subregions express similar theta modulation during trace eyeblink conditioning, or express differences—such as those found in single-neuron recordings—between subregions. We analyzed LFP in the theta band (4-8Hz) in rabbits undergoing trace eyeblink conditioning and 1-month retention testing, and yoked pseudo-conditioned controls. Recordings from dentate gyrus (DG), lateral entorhinal cortex (latEC) and perirhinal cortex (PR) were analyzed. While all three regions showed increased theta amplitude and phase reset to CS (whisker vibration) and US (corneal airpuff) in conditioned animals, the timeline of modulation and results in pseudo-conditioned animals differed. Preliminary findings show a decrease in both amplitude and phase resetting to the CS in PR, latEC and DG after behavioral criterion was reached (>8 conditioned responses per 10 trials), suggesting a role in acquisition, but not retention. Interestingly, the theta response to the US also decreased following criterion in DG, but was maintained throughout conditioning and

post-consolidation in PR and latEC. The response to CS was markedly lower in pseudo-conditioned as compared to conditioned animals in all three regions. Of note, the unpaired US evoked an increase in theta amplitude and phase resetting was maintained over conditioning and consolidation. The theta activity results in DG as well as PR and latEC differ from those reported by our laboratory in CA1, confirming that hippocampal theta is subregion-specific and differentially modulated by time-bridging learning. Changes in activity over the course of learning and between conditioned and pseudo-conditioned animals support differential roles for these MTL regions in forming associations. These findings suggest the need for further studies of hippocampal and parahippocampal slow-wave activity in forebrain-dependent learning.

Disclosures: E.E. Suter: None. **C. Weiss:** None. **J.F. Disterhoft:** None.

Poster

712. Learning and Memory: Aging and Behavior

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Support: NIH Grant 5R37AG008796

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NIH Grant R25 GM121231

Title: Trace eyeblink conditioning in head-fixed mice pairing vibrissae stimulation and corneal airpuff

Authors: L. T. VINSON[1], A. RAPP[1], L. N. MILLER[1], *C. WEISS[2], J. F. DISTERHOFT[2]
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Abstract: Trace eyeblink conditioning (tEBC) has been used as a declarative memory task across species (e.g. humans, rabbits, rats and mice). We have used vibration of the mystacial vibrissae and corneal airpuff to establish a hippocampal-dependent learning paradigm in head-fixed C57BL6 mice to allow for a more in-depth analysis of the neural circuitry involved. In tEBC, a neutral conditioned stimulus (CS), such as vibration of the whiskers, is repeatedly paired with an aversive unconditioned stimulus (US), such as a corneal airpuff, which elicits a reflexive eyeblink response which we detect with subdermal microwires to record electromyographic (EMG) activity from the upper eyelid. The two stimuli are separated by a stimulus free “trace” interval. Acquisition of the tEBC task is evidenced by conditioned responses (CRs), defined as blinks elicited by the CS before onset of the US. Our results indicate that conditioned animals show a higher percentage of CRs compared to those of control animals which received in

random order unpaired CS and US trials. Our results also indicate that the whisker vibration conditioning stimulus (CS) evoked a minimal number of short latency startle responses. This paradigm allows us to set and monitor in real time the amplitude of the vibration CS with a Micro-Epsilon laser-optical displacement sensor. Additionally, the mice are monitored with a webcam to ensure trial presentation only when the animals are not moving (e.g. running, grooming and whisking). The use of whisker vibration and airpuff stimuli will permit the study of learning and memory in aging animals, as other sensory modalities such as vision and audition deteriorate with aging. In addition, these stimuli will allow for *in vivo* recordings during training and following memory consolidation. This mouse based paradigm is ideal for molecular genetic techniques, such as Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) and optogenetics, to be used in future experiments to investigate the role of brain regions including the somatosensory cortex and limbic regions in learning and memory.

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Poster

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Support: NIH Grant R37AG008796

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Title: Cholinergic agonist carbachol reduces the postburst AHP and increases [Ca^{2+}] in CA1 pyramidal neurons of aged rats

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Abstract: The enlarged postburst afterhyperpolarization (AHP) of CA1 pyramidal neurons is hypothesized to be a main source of the learning and memory (L&M) impairments observed in aging subjects (Disterhoft & Oh 2006). Since the AHP is comprised mainly of Ca^{2+}-dependent potassium conductances, the increased cytosolic Ca^{2+} levels ([Ca^{2+}]) during a train of action potentials (APs) observed in aged CA1 neurons (Oh et al. 2013) has also been hypothesized to be a source of L&M deficits. Thus, many studies have focused on reducing Ca^{2+} rise in aged CA1 neurons to rescue the aging-related deficits (Disterhoft & Oh 2007). Other pharmacological manipulations have also been proven to reduce the AHP and rescue aging-related deficits; such

as increasing cholinergic levels with cholinesterase inhibitors in the brain (Disterhoft & Oh 2007). However, it is unknown if AHP reduction and rescued L&M deficits with cholinergic intervention are due to $[Ca^{2+}]$ changes in aged CA1 neurons. Therefore, the present study was designed to determine if bath application of the cholinergic agonist, carbachol, causes a change in $[Ca^{2+}]$ evoked with AP trains in young (3-4 mo) and/or aged (27-33 mo) CA1 neurons from male F344xBN rats.

Whole-cell current clamp and Ca^{2+}-imaging (Oregon Green BAPTA-6F and Alexa 594) data evoked with 100Hz AP trains were collected using a custom built 2-photon laser scanning microscope system before and 20 min after 10μM carbachol was added to the perfusate. Our preliminary data suggest that bath application of carbachol caused ~35% increase in evoked $[Ca^{2+}]$ in aged (n = 10) as compared to ~19% increase in young (n = 8) CA1 neurons. Approximately 13% rise in $[Ca^{2+}]$ was observed in both young (n = 10) and aged (n = 5) CA1 neurons in control experiments. Moreover, carbachol abolished the postburst AHP in both age groups. Minimal change in the postburst AHP was observed in the control groups.

These preliminary data suggest that cholinergic therapeutics that have been shown to rescue aging-related L&M deficits and currently used to slow the progression of Alzheimer's disease (AD) may increase $[Ca^{2+}]$ evoked by AP trains in aging CA1 neurons. This contradicts the major focus of the 'Calcium hypothesis of AD and brain aging', which emphasizes that $[Ca^{2+}]$ be reduced to rescue and/or slow the cognitive decline. Moreover, these data suggest that abolishing the postburst AHP with neuromodulators (e.g., acetylcholine) is a key factor in enhancing $[Ca^{2+}]$ necessary for activating Ca^{2+}-dependent signaling cascades (e.g., gene transcription/translation and cellular machinery) for synapse formation/stabilization as well as altering intrinsic excitability for successful learning and memory formation.

Disclosures: **M.M. Oh:** None. **J.F. Disterhoft:** None.

Poster

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Title: Aging-related changes in the intrinsic excitability of layer III pyramidal neurons of the LEC

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Abstract: Normal aging is often associated with a decline in hippocampus-dependent learning and memory. Previous research has implicated altered intrinsic excitability of hippocampal neurons as mediating these changes in learning ability. In the CA1 region, for example, the intrinsic excitability of pyramidal neurons decreases with aging, as evidenced by an enlarged postburst afterhyperpolarization (AHP). In the CA3 region, on the other hand, there is no difference between the young and aging population in the size of the postburst AHP. CA3 neurons from the aging population, however, can fire more action potentials in response to synaptic stimulation. This increased excitability is mediated by more rapid repolarization due to an enhanced fast AHP (fAHP). The current project focuses on determining whether and how the intrinsic excitability of lateral entorhinal cortical (LEC) neurons changes due to aging. The LEC has been suggested to support hippocampus-dependent temporal associative learning and is also the initial site of manifestation for Alzheimer's disease. The project focuses on pyramidal neurons from layer III, as these neurons project directly to the CA1 of the hippocampus via the temporoammonic pathway. Current clamp recordings were made from layer III pyramidal neurons of the LEC from young adult (3-6-month-old) and aged (29-32-month-old) F1 F344xBN hybrid rats. Our preliminary data indicate that neurons from the aging population (n=6) can fire more spikes in response to increasing depolarizing current injections, relative to neurons from young animals (n=16), despite no difference in the postburst AHP. Neurons from aged animals have a shorter inter-spike-interval (ISI) relative to their young counterparts, which may reflect an enhanced fAHP in the LEC of aged animals. These results suggest that layer III LEC pyramidal neurons undergo similar aging-related intrinsic excitability changes as in the CA3 region of the hippocampus. Although the mean are not significantly different, the data also indicate a separation in the aging population in the postburst AHP, such that there is a population of neurons that have a larger amplitude AHP and another population of neurons with a smaller amplitude AHP. These latter findings suggest a separation in the aging population in terms of learning ability. Experiments are being conducted to test the hypothesis that the smaller postburst AHP comes from a learning unimpaired population and a larger postburst AHP comes from a learning impaired population.

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Poster

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Title: Age differences in ERP correlates of subjective recollection and source memory

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Abstract: In light of the well-attested vulnerability of episodic memory to increasing age, several prior studies have contrasted the ERP correlates of successful recollection in young and older participants, revealing a variety of different findings. Here, we investigated age differences in ERP correlates of subjective recollection according to whether this was accompanied by an accurate or inaccurate source memory judgment. Young (N = 20) and older (N = 20) adults studied concrete nouns while making one of two judgments (fit in a shoebox or manmade). During a subsequent recognition memory test, participants made memory judgments to test words using the RKN procedure. For words receiving a 'Remember' (R) response, a source memory judgment (which study task?) was then required. We examined ERPs elicited on R trials where source retrieval was correct (R+SC), on R trials with incorrect source retrieval or a 'don't know' response (R+SIDK), on 'Know' (K) trials, and on correct rejection (CR) trials. Young, but not older adults, displayed graded (R+SC > R+SIDK > K) left parietal retrieval success effects (500-800ms). Recollection effects in older adults were however dominated by a large, posterior-maximum, negative-going deflection that did not differ according to source accuracy. Both young and older adults demonstrated a positive-going right frontal recollection effect that did not differ with source accuracy (1000-2000ms). Topographic analyses on range-normalized difference ERPs (contrasting memory conditions) indicated significant differences in the scalp distribution of ERP effects for young and older adults in both early (500-800ms post-stimulus) and late (1000-2000ms) time windows. The findings for the young adults are consistent with numerous prior reports that left parietal ERP recollection effects covary with the amount and fidelity of recollected information. More interestingly, the findings provide striking evidence for the engagement of different retrieval processes during recollection in young and older adults.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NIH grant AG046266

S10 OD018132

Title: Sex differences in executive function, stress reactivity, neurochemistry and resting state functional connectivity in middle-aged marmosets

Authors: M. G. LACLAIR[1], N. J. GERVAIS[2], K. P. WORKMAN[2], L. PAYNE[4], C. M. MOORE[4], J. A. KING[4], *A. LACREUSE[3]
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Abstract: The common marmoset (*Callithrix jacchus*) is an increasingly attractive model for aging research. The present data are part of an ongoing longitudinal project investigating sex differences in age-related cognitive decline and their neural correlates in the marmoset. The monkeys (n= 22, 4-6 years old, 11 females) were tested on a battery of tasks assessing cognition, stress reactivity and motor function. A subset was also imaged for Magnetic Resonance Spectroscopy (MRS) and awake resting state functional connectivity (RSFC). Monkeys performed reversal learning and the Intradimensional/Extradimentional (ID/ED) set shifting task, using the Cambridge Neuropsychological Test Automated Battery (CANTAB). Stress reactivity was assessed by separating each monkey from their colony for 7 hours and analyzing urinary cortisol and behavioral measures pre-, during and post- separation. Subjects also performed the Hill-and-Valley task as a measure of fine motor skills. Females were impaired in performing the reversals in both the Reversal Learning task and the ID/ED shifts. Females were also more sensitive than males to the social stressor, as indicated by more agitated locomotion and greater increases in cortisol during separation from the colony. No sex difference was observed for motor skills. Reversal Learning performance was positively associated with glutamate/glutamine (Glx) concentrations in the frontal cortex and this association was stronger in males than in females. Collection of the RSFC data is ongoing. Future studies will determine whether cognitive sex differences and their neural correlates are maintained with increasing age.
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Poster

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Program#/Poster#: 712.09/UU24

Topic: H.01. Animal Cognition and Behavior

Title: Age differences on cognition and emotion related behaviors

Authors: *A. MORA-GALLEGOS, J. FORNAGUERA
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Abstract: On one side, aging is often related to learning and memory decline and on the other side, earlier developmental stages have been related to impulsivity and emotional reactivity. However, there are controversial results and they are also poorly described. In our study, our aim was to compare young (postnatal day 28) and middle-aged male Sprague-Dawley rats (postnatal day 330) performance using different emotional and cognitive tests: open field test (OFT), object recognition (OR) test, active avoidance (AA) and fear conditioning (FC). All rats were tested in OFT and OR but only the half were submitted to AA and the other half to FC tests. In OFT young rats showed more total locomotion, rearing and grooming than middle-aged rats. In OR test middle-aged rats showed a decrease in the exploration of both new and familiar objects, while young rats increased the exploration of both. In AA test, avoidance behavior markedly increased in middle-aged rats along 4 days of test compared to young rats that slightly increased this behavior. In FC test both groups increased time spend on freezing but this behavior differed significantly on training session between age groups, where young rats showed more freezing compared to middle-aged rats. First, these results suggest that young rats have greater emotional reactivity in OFT and FC tests than middle-aged rats who showed a better behavior performance in AA test. In OR test we found opposite trends in the total exploration of both objects between groups but not in the exploration between objects from the first to the second session. Taken together, our results highlight the importance to study different ages to evaluate their performance in different behavioral tests. In this way, we can characterize and better understand the functioning of the nervous system throughout development

Disclosures: A. Mora-Gallegos: None. **J. Fornaguera:** None.

Poster

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Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation

R01 AG049465

Title: Dissociation of performance in hippocampus- and prefrontal cortical-dependent tasks in aging fisher 344 rats

Authors: *N. J. CAREY[1,2], M. A. ZEMPARE[1,2], C. J. NGUYEN[1,2], K. M. BOHNE[1,2], M. K. CHAWLA[1,2], S. SINARI[3], M. J. HUENTELMAN[1,4], D. BILLHEIMER[3], C. A. BARNES[1,2,5]
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Abstract: It is well established that cognition and cognitive performance declines with age-related diseases, but it also declines during normative aging. Even within normal aging, there is a spectrum of performance levels at any given chronological age, where people show differing levels of behavior within a specific age, as well as across ages. This spectrum of decline is also observed in animal models. In this study, we use Fisher 344 (F344) rats of three different ages (young 6mo, middle-aged 15mo, and aged 23mo) in attempt to identify behavioral and molecular markers that may reveal clues to successful cognitive aging. All animals are tested on a thorough cognitive assessment battery to identify their level of performance on multiple domains of behavior that rely on the functional integrity of different brain regions. The first tests are the spatial and cued versions of the Morris water maze, the former relying on the function of the hippocampus, the latter is a test of visual and motor competence. These tests are followed by a spontaneous object recognition task, which relies on the function of the perirhinal cortex. A delayed-match-to-place version of the Morris water maze is then given, to test working memory that is dependent on the prefrontal cortex. Additionally, hippocampus subregion functionality is then assessed using a spatial and temporal ordering task with differing levels of interference. We used the performance level on the spatial version of the Morris water maze task to categorize each animal into a cognitive performance level of low, average, or high, within the young, middle-aged and old age groups. When we used this categorization scheme to group performance on the working memory task, this grouping did not correspond to low, average, and high performance for working memory in the middle aged and older animals, but did correspond to low, average, and high performance for working memory in the young animals. Taken together, these data suggest that beginning in middle-age, the relationship between spatial and working memory performance begins to change: different animals can exhibit a high hippocampal and low frontal cortex performance, low hippocampal and high frontal cortex performance, high performance in both, or low performance in both tasks. This is reminiscent of other data in rats (Bizon et al., 2009) and human studies (Glisky & Kong, 2008) where correlations between hippocampus- and prefrontal cortical-dependent performance is often only weakly related within individuals (Alexander et al., 2012). This suggests that more work is needed to elucidate intervention targets that will be effective for personalized optimization of cognitive aging.

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Poster

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Support: McKnight Brain Research Foundation

R01 AG050548

Title: Deficits in aged rats on the W-track continuous spatial alternation task suggest impaired hippocampal-prefrontal interactions

Authors: *A. J. KAPELLUSCH[1,2,3], A. W. LESTER[2,3], B. A. SCHWARTZ[2,3], J. R. BREWSTER[2,3], C. A. BARNES[2,3,4]
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Abstract: The hippocampus and the PFC are part of a functional system involved in memory-guided decision making, a cognitive process particularly vulnerable to age-related decline in human and animal models of aging. Groups of young and old rats were tested on a continuous spatial alternation task (Frank *et al*., 2000) in which they learned to alternate arm visits on a W-shaped track in order to receive a food reward. There are two interleaved components of this task: (1) an “outbound” or alternation component (working-memory) and (2) an “inbound” component, requiring the animal to remember to return to the center arm (spatial memory). The inbound component is primarily hippocampus dependent. The outbound component, in contrast, likely utilizes both the PFC to maintain a working memory of the previously visited arm, as well as the hippocampus to localize the currently rewarded position in absolute space. Rats with hippocampal lesions are impaired in learning both components of the task and show a pattern of perseverative inbound errors during initial learning (Kim & Frank, 2009). Although lesioning the hippocampus results in slower learning rates, animals are still able to reach learning criterion with time, suggesting adaptive compensation among parallel cognitive networks. Additionally, both aged rats and those with lesions to the mPFC show delayed learning on a T-maze spatial alternation task which also requires rats to maintain a working memory of the previously visited feeder (Ramos *et al*., 2003 , Divac & Wikmark, 1975). In the present study, aged rats made more outbound errors throughout testing, resulting in significantly more days to reach learning criterion, as compared to young rats. Furthermore, while all animals were able to learn the hippocampus-dependent inbound component of the task, 4 of 6 aged animals remained at or near chance level on the outbound component, even after extended testing days. Aged rats may be more impaired on the outbound part of the task because it requires cooperation of both the hippocampus and mPFC, each of which is compromised with age. In addition, there are striking

individual differences among aged animals in their ability to learn this task. The next step in the study will be to perform dual-region ensemble recordings from both the hippocampus and the mPFC while animals complete the alternation task in order to answer how age impacts network dynamics between these two regions, as well as identify the source of significant variation in performance among aged rats.

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Poster

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Support: McKnight Brain Research Foundation

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HHMI 5200006942

Title: Sparser representation of experience by aged rat Lateral Entorhinal Cortex

Authors: *A. COMRIE[1,2], J. P. LISTER[1,4], M. K. CHAWLA[1,2], C. A. BARNES[1,2,3]
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Abstract: The hippocampus undergoes biological changes with age that are related to changes in memory function. Subregions of the hippocampus receive major inputs from and send backprojections to superficial and deep layers of Lateral Entorhinal Cortex (LEC), respectively. In contrast to the well-studied Medial Entorhinal Cortex (MEC), LEC neurons do not show substantial spatial selectivity in their firing patterns. Rather, LEC is thought to be involved in representing non-spatial features of experiences, such as objects and odors. The role of LEC in odor discrimination and how the corresponding neural activity may change with age remain unknown. In this study, we examined whether LEC neuronal populations are selectively activated in response to distinct odors during track running, and hypothesized that aging may alter these activity patterns and contribute to memory dysfunction. To test this, adult and aged rats were trained to run laps on a circular track in a constant environment. After training, one behavioral group (AA) experienced the same set of 6 odors around the track during two run

sessions, separated by 20 minutes. A second group (AB) also had two run sessions, but the odor stimuli were distinct between the two epochs. In principal neurons, the mRNA of the immediate-early gene *Arc* is localized to discrete cellular compartments based on the time since activation. We used cellular compartment analysis of temporal activity by fluorescence *in situ* hybridization (catFISH) and confocal microscopy to visualize this time-dependent subcellular distribution of *Arc* mRNA. We identified neurons activated during the first, second, or both run sessions in superficial and deep LEC. We found that AA and AB behaviors elevated activity in LEC compared to a non-behavioral control condition. However, the population activity failed to distinguish between the distinct A and B odor experiences. This suggests that LEC neural population activity stably represents higher order features of the track-running experience regardless of altered odor input. Surprisingly, more cells reached *Arc* activation thresholds during the second epoch than the first. This may indicate that LEC circuits are sensitive to priming by similar past experience. Additionally, we report that a lower proportion of LEC neurons participated during the behavior in aged rats than in adult rats. This latter result might be explained in at least two ways: the representation of multimodal experience by LEC is either refined or reduced by aging. The question of whether a sparser network representation results in maintained, improved, or reduced behavioral function across the lifespan awaits future investigation.

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Poster

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Support: McKnight Brain Research Foundation

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Alfred P. Sloan Foundation

Title: A separable state-space model of learning across trials and days in an aging study in macaque monkeys

Authors: N. MALEM-SHINITSKI[1], Y. ZHANG[2], D. T. GRAY[3,4], S. N. BURKE[7], *A. SMITH[5,3], C. A. BARNES[3,4,6], D. BA[2]
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Aging,, [6]Dept. of Psychology, Neurology, and Neurosci., [5]Univ. of Arizona, Tucson, AZ; [7]Evelyn F. McKnight Brain Institute, Dept. of Neurosci., Univ. of Florida, Gainesville, FL

Abstract: Understanding how learning and memory changes with normal aging is increasingly important as the aged population grows. Obtaining objective measures of behavioral changes associated with aging is challenging since learning is dynamic, varies considerably between individuals, and observations are frequently binary. We introduce a method for analyzing binary response data from young and aged macaque monkeys performing tasks across multiple days that enables us to compare within-day and across-day performance. The data set comprises 14 female bonnet macaques-6 young and 8 old animals-performing a reversal learning task in the form of a modified Wisconsin Card Sort Task. Conventional methods to analyze these data are unable to capture their inherent two-dimensional nature, fail to distinguish groups, and cannot adequately assess inter-individual differences in performance. We propose a separable two-dimensional (2D) random field (RF) model of the binary data from these experiments, wherein the joint probability of a monkey's correct performance as a function of task and trial depends on two latent Markovian state sequences that evolve separately but in parallel. In this instantiation of the model, we use a Laplacian random walk prior for the monkey-dependent latent process that characterizes the dynamics of a monkey's learning across days. This captures abrupt transitions and allows the detection of change points in the observations across days due to reversal. A Monte Carlo Expectation-Maximization (EM) algorithm is used to maximize the marginal likelihood of the data from the separable 2D RF, followed by a Maximum a Posteriori estimation algorithm for change point detection. The method results in an estimate of performance within a day for each age group, and a learning rate across days for each monkey. We show that as a group the older monkeys find the tasks harder than the young monkeys, and that the cognitive flexibility of the younger group is higher. We further demonstrate the efficacy of the model by using the resulting estimates of performance as features for clustering the monkeys into two groups. The clustering results in two groups that, for the most part, coincide with those formed by the age groups. Simulation studies suggest that clustering based on the model's results captures inter-individual differences in performance levels, which allows us to identify "high performing" old monkeys. These analyses, therefore provide a method to estimate an animal's behavioral/cognitive age independent of chronological age.

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Poster

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Support: McKnight Brain Research Foundation

R37 AG012609

Title: Preserved overall basal firing rates in aged rat basolateral complex of the amygdala, but neurons from aged rats are more engaged in anticipation of rewards compared to young rats

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Abstract: Decision making abilities change across the lifespan as a result of altered brain networks and the accumulation of knowledge and experience. One structure known to be important for detecting changes in value, is the basolateral complex of the amygdala (BLA). Cell numbers in BLA are preserved in aging, but there is a decrease in dopamine transmission as well as receptor density. We recently reported an increase in oscillatory power in the beta-band frequency (~20 Hz) in the BLA, coinciding with the expectation of large rewards in aged rats. We investigated the possibility that the activity of BLA neurons also differs in aged rats during discrimination learning or decision making. To better characterize the activity of BLA neurons in aging, we recorded the single-unit activity of young and aged rats during rest and as they acquired and performed decision making tasks in which reward probabilities and magnitudes were manipulated. Firing properties of BLA neurons during a 30-min rest period before the task was initiated preserved between young and aged rats. During task performance, however, we found that a greater proportion of neurons in the aged rat BLA modulated their firing following entry to the food area (about 2 seconds before reward delivery), whereas the proportion of cells was similar across age groups for all other task events (light cue, lever press and reward). The evoked activity of single neurons was then visualized using peri-event time histograms, and patterns of activation were found to vary in duration, amplitude, sign and onset time. To characterize the firing rate modulation with respect to trial parameters such as reward magnitude and probability, we applied robust statistics to assess the change in firing rate for each neuron individually (at peak firing rate). Using this method, we found that after food cup entry and reward onset, over 20% of BLA neurons in young and aged rats modulated their firing rate to reward size or reward probability, but not trial type (free vs forced choice) nor recent choice history (win/stay-lose/shift). This proportion was greater in aged rats after food cup entry (~35% vs 25%), whereas the proportions were similar across age groups after reward onset (~25%). Finally, we found that more aged rat's BLA neurons displayed greater duration evoked responses following food cup entry (mean 550ms in young and 1650ms in old) and reward onset (mean 1400ms in young and 2700ms in old). Further analyses will investigate the properties of these extended evoked responses. Overall, our results suggest that aging impacts the activity of BLA neurons primarily when animals anticipate or expect rewards, but not as they experience actual rewards.

Disclosures: R.D. Samson: None. **L. Duarte:** None. **C.A. Barnes:** None.

Poster

712. Learning and Memory: Aging and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 712.15/UU30

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation

R01 AG050548

F31 AG055263

Title: The alpha-2 noradrenergic receptor agonist guanfacine impairs flexible attention in young and aged macaques

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Abstract: Prefrontal cortex-dependent cognitive operations are among the earliest to show declines in normative aging. These observations have stimulated interest in developing potential therapeutic interventions to minimize these changes. The alpha-2 noradrenergic receptor agonist guanfacine enhances many prefrontal cortex-dependent behaviors in aged animals, including sustained attention, which involves an animal's ability to focus on one or multiple stimuli for continuous periods of time (e.g., Arnsten and Contant, 1992). Another frontal lobe-dependent process also impaired during aging is known as flexible attention, and becomes engaged when animals serially switch their focus across stimuli (e.g., Clapp and Gazzaley, 2011). It is presently unknown whether guanfacine also improves this form of attention. Because anatomical substrates mediating distinct categories of attention differ across the frontal lobe, as does the relative expression of noradrenergic receptor subtypes, the possibility arises that a given compound could uniquely impact different aspects of attention. The primary aim of this study was to determine whether guanfacine also enhances flexible attention in monkeys. Six young and seven aged macaques were trained to perform delayed nonmatching-to-sample and object discrimination tasks, and were required to switch attention between the two paradigms. Saline or two doses of guanfacine (Low Dose: 0.001 mg/kg; High Dose: 0.05 mg/kg.) was administered prior to testing, and performance with and without drug were compared. The results reveal behavioral impairments in both age groups under both the low and high doses of guanfacine compared to saline. This suggests that flexible attention does not benefit from alpha-2 noradrenergic stimulation like sustained attention does. Thus, guanfacine treatment may be a good option for an individual with deficits in sustained attention, but a bad option for someone

with multitasking deficits. These data argue for person-specific strategies of intervention, ones tailored to an individual's specific pattern of cognitive aging.

Disclosures: D.T. Gray: None. **A.C. Smith:** None. **S.N. Burke:** None. **C.A. Barnes:** None.

Poster

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Support: McKnight Brain Institute

F31 AG055263

RC1 AG06053

Title: Semi-automated layer classification tool for defining cortical architecture

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Abstract: Early cytoarchitectonic attempts to define brain regions were performed wholly on visual cues, i.e., the morphology and distribution of cell bodies and processes throughout nervous tissue as revealed using appropriate staining methods. A variety of attempts have been made to define cortical architecture using quantitative approaches, but despite advances in imaging technology and image processing techniques, for small samples it is still standard practice in most laboratories to identify brain regions in histological samples by hand. This process is labor intensive and introduces variability between observers and fails to scale efficiently with the dramatic expansion in ability to image larger volumes of tissue with cellular resolution. New methods to query the activity of every cell (e.g., CLARITY) within increasingly larger blocks of tissue creates a demand for tools that can remove this bottleneck and automate the process of cortical demarcation. Most previous attempts at quantitative cytoarchitecture have aimed at generating values specific for discrete cortical regions but do not represent the inter-laminar changes within cortical regions themselves. As a first step we report here a semi-automated learning method to delineate cortical layers within a cortical region. Our method utilizes large-scale segmentation of neuronal cell bodies from which we can then extract computed features such as volume, eccentricity, and elongation of the cell body, nearest neighbor

distance, and a variety of staining intensity and texture features. Associative measurements can also be computed and the presence of study-specific biomarkers in association with individually segmented nuclei can be utilized to sort the cells into user-defined classifications (e.g., neuron, glial cell, endothelial cell). In addition to these features, the user defines the contour of the cortical surface, and a depth from this surface is computed for each segmented cell, forming the basis for layer classification using a semi-automated learning algorithm. We have tested the validity of our tool on several fluorescent image datasets acquired from sections of rat entorhinal cortex, collected with a confocal microscope and stitched together into 3D montages, and demonstrated that this classification scheme can sort segmented cells into layers with a distinct combination of morphological values at unique distances from the cortical surface. Our current method, implemented as a component of the FARSIGHT package of image analysis tools, achieved a success rate above 90% in layer classification compared to the results of fully manual layer discrimination by an expert in the field.

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Poster

712. Learning and Memory: Aging and Behavior

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Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation

R37 AG012609

F31 AG055263

Title: Age-associated changes in awake hippocampal sharp-wave ripples during spatial eyeblink conditioning

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Abstract: Sharp-wave ripples are brief (~70 ms) high-frequency oscillatory events that are generated in the hippocampus. Ripples that occur during rest periods following a learning experience are believed to support memory consolidation. Normal aging reduces the rate of occurrence of ripple events and reduces the oscillatory frequency of ripples during rest (Wiegand et al., 2016). Although ripples during rest have been implicated in memory consolidation,

waking ripples may also be involved in short-term planning and memory recall. It is unknown how normal aging alters features of waking ripples. Accordingly, we investigated whether characteristics of waking ripple oscillations and associated single-unit activity undergo age-dependent changes in rats. Local-field and single-unit activity were recorded from the CA1 region of the hippocampus. Sharp-wave ripple events were examined in old (n = 5) and young (n = 6) F344 male rats as they performed a place-dependent eyeblink conditioning task. Comparisons between ripples occurring during rest and waking behavior and between aged and young animals revealed two effects. First, although ripples in aged rats had a significantly lower oscillatory frequency relative to young rats during rest ($p < 0.01$, t-test, n aged = 5, n young = 6), there was no difference between aged and young rats on this measure during behavior ($p = 0.83$). Second, the modulation of principal neuron firing activity by waking ripples was reduced in aged animals when compared to young rats (aged: n = 233 neurons, young: n = 167 neurons, Wilcoxson rank sum test, $p < 0.001$). Modulation was measured as the difference between the mean firing rate during the ripple compared to the mean firing rate during 100 ms intervals that preceded and followed each ripple (+/- 350 to 450 ms). Even though ripple oscillatory frequency was normalized in aged rats during behavior, modulation of single cell activity within a ripple was reduced. Given the involvement of waking ripples in memory recall, these changes in the dynamics of waking ripples could contribute to age-associated memory loss.

Disclosures: S.L. Cowen: None. **D.T. Gray:** None. **J. Wiegand:** None. **L.A. Schimanski:** None. **C.A. Barnes:** None.

Poster

712. Learning and Memory: Aging and Behavior

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Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation

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P30 AG019610

Title: Dynamic expression of RNA stress granule components in aging brains: From flies to rats

Authors: B. BAGEVALU SIDDEGOWDA[1], M. K. CHAWLA[2,3], S. YAO[1], C. A. BARNES[2,3,4], *D. C. ZARNESCU[5,1]
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Abstract: RNA stress granules are dynamic cytoplasmic structures that assemble in response to various cellular insults. In the process, these non-membrane bound organelles sequester specific mRNAs causing inhibition of translation initiation, with the goal of protecting the cell from spending precious resources during times of stress. Upon stress removal, RNA stress granules disassemble and translation is reinitiated. These dynamic changes in RNA stress granules have been linked mechanistically to age-related neurodegenerative diseases suggesting that they may be playing key roles in the aging process. Despite some existing reports that translation inhibition changes with aging, it remains unclear whether RNA stress granules are undergoing dynamic changes as organisms grow older. To shed light on this question, we began by profiling the expression of RNA binding proteins associated with RNA stress granules including TIAR, PABP, FMRP, Gcn2 as well as the translation initiation factor eIF2alpha in aging fly and rat brains. Analyses of both transcript and protein expression of these RNA stress granule/translation initiation markers indicate dynamic changes in aging fly and rat brains. While Gcn2 and phosopho-eIF2alpha expression decline, there is an increase in TIAR levels with age. In addition, the expression of TAR DNA binding protein (TDP-43), a key RNA binding protein implicated in neurodegeneration exhibits a reduction in expression in both fly and rat brains, during aging. These findings support the hypothesis that RNA stress granules undergo dynamic changes during aging. Current experiments including polysome fractionations and expression profiling are aimed at elucidating the role of cellular stress responses in aging brains from the perspective of RNA stress granules.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation

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Title: Brain region-specific changes in melanocortin receptor expression in aged rat brain

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Abstract: It has been reported that the human melanocortin 4 receptor (hMC4R) is involved in neurodegenerative disease (Shen et al., 2016). Melanotropins may protect against the progression of Alzheimer's disease (Giuliani et al., 2014). Furthermore, administration of α-MSH or its more stable analog [Nle^4,D-Phe^7]-α-MSH (NDP-α-MSH) has been observed to enhance learning and memory (Beckwith, et al. 1975). However, the impact of age with respect to melancortin receptor expression remains unexplored. Here we systematically investigated the expression of melanocortin receptors in brain of young (9 months) and aged (23 months) rats, who were assessed for their cognitive status in memory tasks. Six regions of the brain were extracted from each animal, including the frontal cortex + anterior midbrain, parietal cortex, cerebellum, posterior midbrain, hippocampus and occipital lobe. We collected the membrane fragments from each region of all animals in each age group, then ran a specific binding assay using iodine labelled NDP-α-MSH on a high throughput Micro Beta II radiation counter. Six samples were measured from each animal for each region, and then averaged to produce a single count for each animal in each region. All measurements were collected in a blind fashion. We discovered that melanocortin receptor expression was reduced in the aged rats in four of the six regions studied. This finding potentially opens a new window of discovery for exploring and developing new treatments for cognitive changes that arise in normal aging and in neurodegenerative disease.

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Poster

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Support: McKnight Brain Research Foundation

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R01 AG050548

Title: Temporal contiguity predicts reward association learning in bonnet macaques

Authors: *C. KYLE[1], A. C. SMITH[1], D. T. GRAY[1], S. N. BURKE[4,5], C. A. BARNES[1,2,3]
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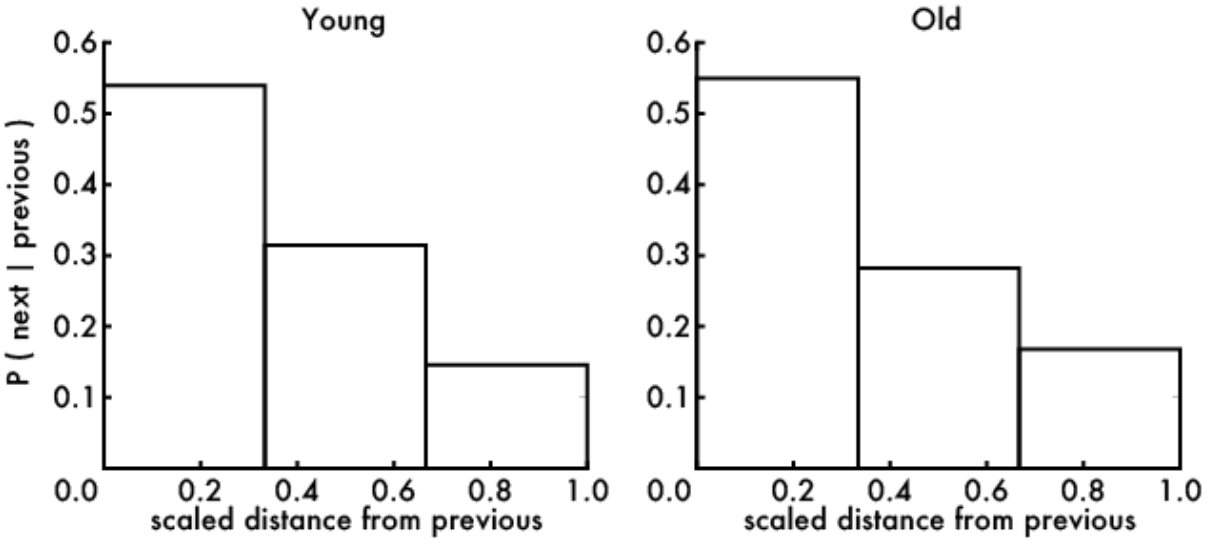
Abstract: When human subjects freely recall items from a list, they are more likely to name a neighbor of the item they last recalled. This finding, known as the temporal contiguity effect, has

led to the development of the “temporal context model” of memory which theorizes that temporally neighboring events share similarity in the underlying neural representations (Howard and Kahana, 2002). While this model is supported by studies examining brain activity using local field potential or functional MRI measurements in humans (Hsieh et al., 2014, Kyle et al., 2015, Manning et al., 2011), because only humans can perform free recall, the scope of research on this topic has remained limited. However, state-space models, which through Bayesian statistics can uncover the precise timing of learning, make it possible to investigate temporal contiguity in tasks that do not rely on verbal responses. Here we utilize a state-space model and new methods to calculate the conditional probabilities in a fixed-sequence, forced-choice reward association task performed by 16 bonnet macaques. The results suggest that during multiple days of association-pair learning, newly-learned pairs tend to be more temporally contiguous to recently-learned pairs than to more distant pairs in both young (10 yrs, n=7) and old (23 yrs, n=9) monkeys {figure below}. To our knowledge, our data represent the first evidence that temporal contiguity can underlie reward association learning and extends the study of contiguity using conditional probabilities to non-verbal tasks.



Disclosures: **C. Kyle:** None. **A.C. smith:** None. **D.T. Gray:** None. **S.N. Burke:** None. **C.A. Barnes:** None.

Poster

712. Learning and Memory: Aging and Behavior

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Support: McKnight Brain Research Foundation

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R01 AG050548

Title: An alternative to dye-based approaches to remove lipofuscin-induced background autofluorescence from primate brain tissue

Authors: W. PYON[1,2], D. T. GRAY[1,2], M. K. CHAWLA[1,2], *C. A. BARNES[1,2,3]
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Abstract: Lipofuscin results from the collection of lipid residues in lysosomes within cells throughout the body, including neurons. An accumulation of this pigment is one of the most consistent findings across age in the brains of primates with its appearance being correlated with chronological age. This process has generally been considered to be the result of normal cellular "wear-and-tear." Such age-related pigment accumulation, however, presents challenges for fluorescence-based cell quantification in the midbrain since these pigment molecules possess fluorescent emission spectra that invade the normal collection range of most fluorescent microscopes. The use of fluorescence microscopy for anatomical studies has multiple benefits including the ability to label multiple fluorophores, which necessitates a standardized procedure for reducing the background effects of neurolipofuscin-induced autofluorescence that can obscure relevant fluorescent signals. Current strategies to combat such autofluorescence include the use of lipophilic dyes to mask native fluorescent emission from brain tissue (Schnell et al., 1999; Romjin et al., 1999). While these dyes successfully remove autofluorescence, they also degrade the emission of fluorophores commonly used in immunofluorescent microscopy. Here we present an alternative method for removing lipofuscin-induced autofluorescence. This strategy involves defining lipofuscin's emission spectrum given laser lines ranging from 405nm - 633nm on a Leica SP5-II spectral confocal microscope. These spectra are used to subtract lipofuscin-based autofluorescence from fluorescent channels commonly used in immunofluorescent studies. This collection protocol reliably diminishes native autofluorescence while preserving the fluorescence of tyrosine hydroxylase- and calbindin-immunolabelled cells in the ventral tegmental area of young and aged rhesus macaque brains. Here the autofluorescence subtraction procedure is compared to the standard method (Sudan Black B protocol) in order to evaluate which technique most successfully reduces autofluorescence while maintaining the integrity of relevant fluorescent signals.

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Poster

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Altschul foundation

VA Career Scientist Award

Title: Role of wine derived polyphenolics as novel epigenetic modifiers in age related cognitive impairment. From responsible nutrition to promotion of neuroresilience

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Abstract: Modifiable lifestyle factors such as moderate red wine intake are receiving increasing attention in their potential preventative impact on mechanisms associated with progression of Alzheimer's disease cognitive decline. The mechanisms through which brain bioavailable red wine derived phenolic acids exert their beneficial effects in humans has been strongly investigated in relation to microbiome metabolism and demonstrated that certain microbes from intestinal flora generate phenolic acids able to improve cognitive decline (Ho *et al*., 2014) . We continued to characterize several bioactive polyphenol metabolites and gut derived phenolic acids *in vitro* as potential epigenetic modifiers that might influence long term nutritional benefits in response to grape derived phenolic acids. Interestingly we found that mRNA expression of DNA *de novo* methylation enzyme DNMT3b is significantly decreased ($p< 0.05$) while the expression of the DNA hydroxymethylation enzyme TET2 ($p<0.05$), but not TET3, is increased following treatment with quercetin-3-O- glucuronide (500 nM, 72 hr) in primary embryonic cortico-hippocampal neuronal cultures. We also found that the microbiome derived phenolic acids 3-hydroxybenzoic acid and 3-(3'-hydroxypheyl) propionic acid (10µM, 72 hr) significantly promoted TET2 ($p<0.05$) expression. After bioavailability and structural identification of polyphenols, we continued to validate our findings *in vivo*. Excitingly, we found that the expression of DNMT3a ($p<0.01$), DNMT3b ($p<0.05$) TET2 ($p<0.05$) and TET3 ($p<0.01$) is selectively decreased in the hippocampal formation of mice following oral administration of a standardized bioavailable bioactive dietary polyphenolic preparation (BDPP). While this study strongly supports the need to further dissect select BDPP components, they also support ongoing investigations regarding the role of DNA methylation in response to bioavailable polyphenol metabolites and gut-derived phenolic acids. Based on this evidence using representative bisulfate

sequencing approaches we are currently sequencing at base-pair resolution for methylated CpG sites to further investigate novel dynamic methylation of the genome in mice treated with BDPP. The outcome of this study therefore provides for the first time a stepping stone to generate wine/grape based mimetic probiotics to promote resilience via brain bioavailable polyphenol metabolism against age-related psychological and cognitive impairment which we found may involve long term responses through epigenetic mechanisms.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: CalciGenix

Title: Apoaequorin differentially modulates fear conditioning in adult and aged rats

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Abstract: The population of aging individuals worldwide is dramatically increasing. Although advancing age is associated with increased risk for dementia, the elderly may also suffer from cognitive impairment in the absence of dementia. The study of learning and memory can tell us how information processing changes as a function of aging, and can be a vital tool for understanding aging-related cognitive decline. Animal studies have demonstrated that aging is accompanied by impaired hippocampal-dependent associative learning. For example, aged rodents demonstrate impaired trace and context fear memory. A proposed contributor to these learning and memory deficits is dysregulation of neuronal calcium. Normally, cells are able to regulate calcium levels by utilizing calcium-binding proteins (CaBPs), but expression of these proteins is reduced in aged animals. One CaBP that has demonstrated neuroprotective properties is apoaequorin (AQ), a protein isolated from the jellyfish *Aequorea victoria*. Data from our lab indicate that direct infusion of the AQ protein into the dorsal hippocampus prior to an *in vitro* ischemic insult reduces cell death. Thus, our question was whether infusion of AQ into dorsal hippocampus could effectively mitigate aging-related fear memory deficits. In our initial experiment, adult and aged rats were randomly assigned to receive a bilateral dorsal hippocampal infusion of vehicle (Adult-Veh; Aged-Veh) or AQ (Adult-AQ; Aged-AQ) one day prior to trace fear conditioning. All rats were tested one day following conditioning. During the test, Aged-

Veh and Aged-AQ rats froze significantly less than Adult-Veh and Adult-AQ rats ($p < .05$), suggesting infusion of AQ does not rescue aging-related trace fear memory deficits. In our next set of experiments, we sought to determine whether AQ infusion could induce state-dependent learning in either age group by infusing it 1 h before conditioning and testing. Adult and aged rats were randomly assigned to one of four infusion groups: vehicle pre-training and pre-testing (Veh-Veh), vehicle pre-training and AQ pre-testing (Veh-AQ), AQ pre-training and vehicle pre-testing (AQ-Veh), and AQ pre-training and pre-testing (AQ-AQ). While AQ infusion prior to training and testing did not mitigate trace fear memory impairment in aged rats, aging-related context fear memory impairment was not significant ($p = .1$), suggesting AQ infusion induces a state-dependent enhancement of context fear memory. The results of these experiments implicate a role for AQ in the modification of cognitive function in aged rats.

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Poster

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the Brain Mapping by Integrated Neurotechnologies for Disease Studies from the Ministry of Education, Culture, Sports, and Technology in Japan

Title: Deterioration of visual discrimination learning in aged marmosets

Authors: A. TAKEMOTO[1], E. L. MUNGER[2], M. RAGHANTI[3], *K. NAKAMURA[1]
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Abstract: Learning and memory processes are similarly organized in humans and nonhuman primates. Therefore, behavioral and cognitive studies in nonhuman primates can be used to understand human learning and, in particular, the effects of aging on cognitive processes. Macaques have been widely used in cognitive learning research, though recently common marmosets (*Callithrix jacchus*) have been suggested as a nonhuman primate model for aging and neuroscience research. However, the effect of aging on cognition has been poorly studied in this species. The present study examined the effects of age on the ability of common marmosets to

learn visual pattern discrimination tasks and reversal learning. Four research-naïve marmosets aged ten years or older participated in this study (2 males and 2 females). For the visual discrimination learning, two different square graphic pattern stimuli (27 mm x 27 mm) were presented either to the left or right of center on the touch screen. One image, if touched, would provide the marmoset with a reward and a tone where the other would not. The marmosets would complete a single session of 100 trials per day. The marmoset would continue with the same visual discrimination learning experiment until 90 correct responses out of 100 trials in one day were achieved. Once the marmoset reached the learning criterion, a new learning task was presented the following day. The marmosets in this study completed three visual discrimination learning experiments (N1, N2, N3) followed by a reversal learning (R3). Once the 90% criterion was reached in the first reversal learning, the marmosets completed a fourth visual discrimination (N4) followed by a second reversal learning (R4). We found that aged marmosets commit significantly more errors in the initial stages of visual discrimination and more perseverative errors in reversal learning, indicating prefrontal dysfunction. On the other hand, they showed comparable performance with the younger marmosets in the later stages. Our present data demonstrate that marmosets can be good nonhuman primate model for aging.

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NIH R01-AG052934

University of Michigan Protein Folding Diseases Initiative

Title: Does acarbose treatment differentially modulate cognitive healthspan with respect to age, genetic background, or neurodegenerative disease?

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Abstract: As an increasingly large segment of society reaches the oldest age brackets, there is growing interest in identifying treatments that can slow or eliminate distinct aging processes. These clinical interventions may extend lifespan, improve mobility, or preserve cognitive

function, any or all of which may both increase the quality of life for the individual as well as reduce the global health care burden.
Acarbose has been identified by the National Institute on Aging's Interventions Testing Program as a drug which significantly extends lifespan in a genetically heterogeneous mouse line, UM-HET3. Because acarbose is already used in a clinical capacity in humans and is known to be safe and well-tolerated, it has the potential for rapid translation into clinical studies. Therefore, we investigated whether acarbose was also effective in improving or preserving cognitive function in young and middle-aged wild-type (WT) mice and those harboring five familial Alzheimer's disease (AD) mutations on the UM-HET3 genetic background. Our previous data suggested that acarbose treatment improved learning and memory performance (as assayed by the Morris Water Maze) in both WT and AD mice compared to those maintained on control chow, at least at 9 months of age.
Our current work expands the scope of these previous studies in two important respects: 1. We extend our investigation to significantly older ages by testing whether acarbose treatment improves cognitive function in aged WT and AD UM-HET3 mice at ~24 months old; and 2. We examine the generalizability of the effectiveness of acarbose treatment by assaying cognitive function in 9 month-old WT and AD mice on a C57Bl/6 genetic background. Together, these new studies will further elucidate the potential of acarabose as a therapeutic intervention aimed at ameliorating cognitive decline in the aging population and in those affected by neurodegenerative disease.

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Poster

712. Learning and Memory: Aging and Behavior

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 712.26/UU41

Topic: H.01. Animal Cognition and Behavior

Title: Specific behavioral and cognitive changes in mouse models of different neurodegenerative diseases and normally aging mice

Authors: *B. KOOPMANS[1], S. SPIJKER[2], R. E. VAN KESTEREN[3], M. VERHAGE[4], A. B. SMIT[5], M. LOOS[1]
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Abstract: Detailed knowledge on the age-of-onset of behavioral abnormalities in mouse models of neurodegenerative diseases could facilitate our understanding of the early sequence of events

leading to neurodegeneration and may create a window of opportunity for preclinical testing of prophylactic treatments. Earlier studies by us and others showed that undisturbed behavior of individually housed mice in a home-cage environment equipped with a shelter is highly discriminative between mouse strains. To identify changes in home-cage behavior that are specific for different neurological symptoms in neurodegenerative disease models, we analyzed mouse models with pure motor function deficits and/or cognitive deficits, and compared their behavioral profiles with ageing C57BL/6J mice. For this systematic analysis AHCODA-DB was used, a data repository with web-based mining tools for the analysis of automated high-content mouse phenotypic data. Ageing C57BL/6J mice showed a profound decrease in general activity with increased age. In contrast, mouse models that developed strong motor function deficits by 20 weeks, including the SOD1*G93A mouse model of amyotrophic lateral sclerosis (ALS) and a model of Tau pathology, showed rather specific changes in activity parameters (e.g. maximum velocity) when compared to age-matched wild-type controls. Interestingly, SOD1*G93A mutant mice displayed alterations in sheltering behavior as early as 12 weeks of age, preceding pathology. Furthermore, whereas ageing C57BL/6J mice showed a strong deterioration of their circadian pattern with increasing age, this was not evident in mouse models of Alzheimer's disease at ages when pathology is present (6 months and older). Mouse models with cognitive function impairments, including two models of Abeta (Aβ) toxicity (APP/PS1 and 5xFAD) showed specific changes in the distribution of short visits to their shelter, already at ages when no pathology was present. In conclusion, different aspects of home-cage behavior are sensitive to different neurological conditions, and are clearly distinguishable from normal ageing. Most importantly, several changes were detected at early ages when classical pathology is not evident, suggesting that alterations in home-cage behavior reflect molecular or cellular changes that precede classical pathology.

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Poster

712. Learning and Memory: Aging and Behavior

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 712.27/UU42

Topic: H.01. Animal Cognition and Behavior

Title: The early life immune stimulation induces a sex differences in long lasting modifications in cognitive behavior in middle aged rats

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Abstract: Background: Aging is one of many factors associated with an increased susceptibility to neurodegenerative disorders which can be related to early life inflammation. Early life immune stimulation, however, can be characterized by the increase in cytokines, oxidative stress as well as changing in microglia phenotypes from activated to priming during the age. Indeed the early neuroinflammation can profoundly affect brain function which can elicit behavioral impairments and cognitive deficits.
Objective: The aim of our study is to explore the sex differences and the possibilities to accelerate the cognitive decline associated with aging after a neonatal immune stimulation.
Methods: Male and females Wistar rats were treated on a postnatal day 14 with PBS or LPS, and then tested for learning & memory at 3 or 10 months of age, using novel object, Y-maze, and a spatial water maze task.
Results: Neonatally-infected rats exhibited memory impairments in the water maze, but only at 10 months. And no significant differences in novel object and Y-maze. Neonatally-infected rats also exhibited greater aging-induced increases in a number of microglia-activating in DG, CA1, and CA3, as well as an increase in Nitrite Oxide and lipid peroxidation but not TNFα within the hippocampus, but not in prefrontal cortex compared to controls.
Conclusion: Taken together, these data suggest that early-life infection leads to less successful cognitive aging, which may be linked to changes in microglial reactivity.
Key words: neuroinflammation, Aging, neurodegenerative

Disclosures: I. Berkiks: None. **A. el hessni:** None. **A. mesfioui:** None.

Poster

713. Perceptual Decision Making

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Topic: H.02. Human Cognition and Behavior

Support: German Research Foundation (DFG), DO 1240/3-1

DFG, SFB 936/A7

Title: Pupil-linked arousal adjusts the perceptual decision process to changing environments

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Abstract: Many decisions involve the temporal accumulation of evidence in favor of each available alternative. To make optimal choices in different environments, decision-makers must be able to flexibly adjust two components of this accumulation process: (i) the criterial level of

cumulative evidence required for decision commitment ('decision bound') and (ii) the timescale (or 'leakiness') of the accumulation. The mechanisms underlying either type of adjustment are not known. Here, we examined whether pupil-linked arousal, which regulates global brain state and modulates decision-related neural dynamics, helps adjust the decision bound or accumulation timescale to changing environmental statistics. Thirty human subjects monitored two patches of fluctuating luminance, one on each side of fixation, and were asked to report the location of near-threshold increments in mean luminance (the 'signal') embedded in longer streams of dynamic noise. We compared two conditions that differed in the distribution of signal durations: one with predominantly short (150 ms) and another with predominantly long (900 ms) signals. Simulations from an accumulator model showed that reward maximization on this task necessitates adjustments to both decision bound and accumulation timescale between conditions: when signals tend to be short, one should adopt a lower decision bound and shorter time constant. By contrast, analysis of observed behavior, psychophysical kernels and model parameter estimates indicated that while subjects strongly adjusted their decision bound, there was no adjustment of timescale in the expected direction. Pre-trial pupil diameter, a proxy for central arousal state, changed with environmental context and predicted behavioral adjustments. Pupil diameter was larger when signals were predominantly short (the context associated with lower decision bounds); and, this increase in pupil diameter predicted the context-related change in signal detection rate and response time in ways that support an association between pupil-linked arousal and decision bound adjustment. Trial-to-trial fluctuations in pre-trial pupil diameter also predicted the same behavioral metrics within each environmental context. Our results indicate that pupil-linked arousal helps adjust decision bounds. This adjustment might be implemented via global changes in synaptic gain, consistent with the neuromodulatory properties of pupil-linked arousal systems. The lack of timescale adjustment contrasts with recent results from a less demanding version of the same task (Ossmy et al, *Curr Biol*, 2013).

Disclosures: **P. Murphy:** None. **T. Pfeffer:** None. **K. Tsetsos:** None. **T.H. Donner:** None.

Poster

713. Perceptual Decision Making

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: German Academic Exchange Service (DAAD)

German Research Foundation (DFG), DO 1240/3-1

German Research Foundation (DFG), DO 1240/2-1

German Research Foundation (DFG), SFB 936/Z

Title: Choices bias the accumulation of perceptual evidence in the next trial

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Abstract: Perceptual choices under uncertainty are biased by previous choices, a phenomenon referred to as serial choice bias. We aimed to uncover how this bias affects decision dynamics, as described by the accumulation of noisy sensory evidence towards opposing bounds for each choice option. We used the drift diffusion model (DDM) to disentangle two possible biasing mechanisms: an offset of the accumulation *starting point*, or a bias in the *drift* (accumulation rate) towards one of the choice bounds.
We fit a hierarchical DDM to four different data sets, all involving random dot motion discrimination tasks in humans (total: N = 201): (i) up vs. down (fixed motion coherence near psychophysical threshold) reaction time task; (ii) up vs. down (varying coherence levels) fixed duration task with different stimulus repetition probabilities (0.2, 0.5, 0.8, blocked by session); (iii) 2-interval forced choice coherence discrimination (varying coherence increments/decrements); (iv) as (iii), but fixed coherence increments/decrements near threshold. We estimated the following model parameters: non-decision time, starting point, boundary separation, mean drift rate, drift rate variability, and an additive drift bias. In different versions of the model, starting point, drift bias, or both were free to vary with previous choices and stimuli, and formal model comparison was used for model selection.
The DDM fit all data well, including those from fixed duration tasks. The estimated mean drift rate depended lawfully on evidence strength and correlated with perceptual sensitivity (d'). Across data sets, model fits improved by incorporating serial choice bias, where the predominant effect of previous choice was on drift bias. When stimuli predominantly alternated or repeated, the drift bias and (to a lesser extent) starting point tracked these biased serial statistics. When stimulus sequences were random (repetition probability of 0.5), drift bias (without starting point bias) was sufficient to account for serial choice patterns. In all data sets, the effect of previous choice on drift bias correlated with the model-free proportion of choice repetitions. For starting point, this correlation was weaker or absent. Reaction time, a measure of decision uncertainty (Urai et al. 2017), reduced the impact of choices on subsequent drift bias.
We conclude that the history of choices primarily biases evidence accumulation towards a particular choice option. This contrasts with biases induced by manipulations of stimulus frequency or payoff, which primarily shift the starting point of evidence integration. These insights put constraints on the neural basis of serial choice bias.

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Poster

713. Perceptual Decision Making

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European Commission (Marie Skłodowska-Curie Individual Fellowship, CH2020), 658581-CODIR

Title: GABAergic competition boosts the irrationality of human decision making

Authors: *K. TSETSOS, T. H. DONNER
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Abstract: Humans often violate the principles of rational choice theory. For instance, they may prefer *A* over *B*, *B* over *C* but *C* over *A*, disclosing thus inconsistent preferences. Such violations of decision rationality imply that the valuation of an alternative is *context-sensitive*, being influenced by the properties of other available alternatives. This context-sensitivity has been recently attributed to a *selective gating* mechanism: In choice tasks requiring the accumulation of temporally discrete psychophysical or numerical samples, momentarily less-valued samples are accumulated with a lower gain (Tsetsos et al., *PNAS*, 2012; 2016). We hypothesized that this gating is mediated by intra-cortical competition among incoming samples through GABAergic inhibition. We tested this hypothesis by combining placebo-controlled pharmacological manipulation of $GABA_A$ receptors (boosting intra-cortical inhibition) with computational modelling of choice behaviour in a numerical integration task.
Human participants (*N*=32) performed 3 sessions, the first one without pharmacological manipulation, followed by two sessions after intake of lorazepam (1 mg) or placebo (order counterbalanced). On each trial, participants observed pairs of numerical values presented rapidly (1.25 HZ) and sequentially, to the left and right of a central fixation point. The sequence stopped after a fixed number of pairs (5-8), and participants had to judge which side had the higher average. In a subset of trials, we controlled the temporal distribution of values to quantify context-sensitivity. Choice behavior was modeled using a sequential sampling model, in which the incoming values are dynamically transformed (by inhibiting each other) and continuously fed forward (“in cascade”) into choice accumulators.
Choice accuracy did not differ between drug and placebo sessions. However, diagnostic

behavioral signatures of context-sensitivity increased under lorazepam. Fitting the model explained the $GABA_A$-induced elevated context-sensitivity as a consequence of increased mutual inhibition at the level of input representation. By contrast, other decision-relevant model parameters, specifically internal noise or the time constant of value accumulation, were not affected by the pharmacological intervention.
Our results illuminate the neural basis of context-sensitive valuation phenomena (and by extension decision irrationality), linking these behavioral phenomena to competitive dynamics that have been observed in other domains of cortical computation, such as multi-stable perception (van Loon et al, *Curr Biol*, 2013).

Disclosures: K. Tsetsos: None. **T.H. Donner:** None.

Poster

713. Perceptual Decision Making

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Title: Dissociated catecholaminergic and cholinergic shaping of large-scale cortical correlations

Authors: *T. PFEFFER[1], A. PONCE-ALVAREZ[2], G. NOLTE[1], R. L. VAN DEN BRINK[3], S. NIEUWENHUIS[3], A. K. ENGEL[1], G. DECO[2], T. H. DONNER[1]
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Abstract: The catecholaminergic (noradrenergic and dopaminergic) and cholinergic systems have long been implicated in the regulation of brain states and behavior. The brainstem centers of these systems have widespread projections to most parts of the cortex. Influential theories

postulate that these neuromodulatory systems play important, and distinct, computational roles in learning, inference, and decision-making. Yet, it remains unknown how these systems shape the large-scale cortical dynamics underlying cognition and behavior. Here, we unravelled and compared the effects of catecholamines and acetylcholine on the large-scale correlations of intrinsic neural dynamics in the human brain.
We boosted catecholamine (using atomoxetine) or acetylcholine (using donepezil) levels through selective pharmacological interventions (randomized, placebo-controlled, cross-over design) in 28 healthy human subjects. We measured the effects on intrinsic cortical dynamics with magnetoencephalography (MEG), during two steady-state conditions: blank fixation ('rest') and covert counting of bistable perceptual alternations under continuous visual drive, in the absence of motor movement ('task'). Subjects were administered placebo, atomoxetine, or donepezil before MEG in separate sessions. MEG was recorded during two rest and two task blocks (a 10 min), in counterbalanced order. MEG sensor level signals were projected onto 90 regions of the AAL (Automated Anatomical Labelling) atlas using adaptive linear spatial filtering ('beamforming'). We correlated the amplitude envelopes of neural signals in several frequency bands between all 90 regions, controlling for volume conduction by orthogonalization of the underlying carrier signals.
We find that catecholamines *increased* cortex-wide amplitude envelope correlations in the alpha-band (~11 Hz), but only during constant visual drive (task) and not during blank fixation (rest). By contrast, acetylcholine *decreased* cortex-wide amplitude envelope correlations, but only during blank fixation and not during visual drive. Our results reveal a context-dependent dissociation between the large-scale effects of key neuromodulators on human cortical dynamics. We next plan to uncover the biophysical mechanisms explaining this dissociation through large-scale computational modeling.

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Poster

713. Perceptual Decision Making

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: German Research Foundation (DFG), DO 1240/3-1

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Title: Computational and neuromodulatory correlates of pupil dilation during perceptual choice

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Abstract: Brainstem neuromodulatory systems respond phasically during decisions (Aston-Jones & Cohen, *Annu Rev Neurosci*, 2005). At different times during a decision, these responses signal two computational variables that are key for decision-making: (i) decision uncertainty before feedback and (ii) prediction errors (i.e., deviations from expected outcomes) after feedback (Lak et al., *Curr Biol*, 2017). Responses in several brainstem systems correlate with pupil dilation (de Gee et al., *eLife*, 2017). Here, we aimed to pinpoint the computational variables and neuromodulatory brainstem systems driving pupil responses during decision formation and after feedback about decision outcome.
Fifteen human subjects performed an up vs. down motion discrimination task, with two difficulty levels and feedback, during functional magnetic resonance imaging (fMRI) and eye tracking. After a variable delay (4-12 s) following choice, we presented visual feedback that was coupled to a monetary reward. Motion coherence varied from trial to trial, so that observers performed at 70% correct in 2/3 of trials ('hard') and at 85% correct in 1/3 of trials ('easy'). Physiological noise was removed from the fMRI data using a previously established protocol (de Gee et al., 2017).
Pupil dilation before and after feedback was modulated by decision difficulty (hard vs. easy) and accuracy (correct vs. error), exhibiting significant interactions between both factors. In line with previous findings (Urai et al., *Nature Comm*, 2017), this interaction reflected the level of decision uncertainty prior to feedback. After feedback, the interaction reflected (the inverse of) a prediction error signal. Pupil dilation before and after feedback was qualitatively in line with a partially observable Markov decision process (Lak et al., 2017). Further, both components of the pupil response were coupled to fMRI responses in several modulatory brainstem centers: the noradrenergic locus coeruleus, dopaminergic midbrain nuclei, cholinergic basal nucleus, and serotonergic raphe nuclei (even after accounting for their co-correlations). The locus coeruleus was only coupled to pupil dilations before (not after) feedback. During both intervals, we also found robust pupil-linked fMRI responses in the striatum, which receives strong dopaminergic but no (or only sparse) noradrenergic input.
Our results shed new light on the computational processes and neuromodulatory centers driving evoked pupil-linked arousal boosts during decision-making under uncertainty. They also point to a significant non-noradrenergic (specifically: dopaminergic) component of pupil dilation.

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Poster

713. Perceptual Decision Making

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German Research Foundation (DFG), DO 1240/3-1

German Research Foundation (DFG), SFB 936 Projects A2/A3, A7

Title: Cortical dynamics reflecting Bayesian uncertainty and surprise about the timing of perceptual events

Authors: *T. MEINDERTSMA[1,2,3], N. A. KLOOSTERMAN[1,2,4], A. K. ENGEL[3], E.-J. WAGENMAKERS[1], T. H. DONNER[1,2,3]
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Abstract: Knowledge about the timing of relevant events in the sensory environment can benefit decision-making. Several subcortical brain regions seem to be driven by uncertainty about event timing, as well as violations of timing expectations (‘surprise’). Less is known about how the temporal statistics of the environment affect the dynamics of cortical networks that mediate sensory-motor decisions. Here, we used magnetoencephalography (MEG) to exhaustively map the trial-to-trial correlation between variations in uncertainty or surprise about event timing and cortical dynamics in a simple visual decision task.
28 human subjects judged (by button press or after silently counting) the on- and offsets of a salient visual target (full contrast Gabor) surrounded by a moving distractor. The intervals between the perceptual events varied randomly from trial to trial (hazard rates following either Gaussian or uniform distribution, on different blocks). We used a Bayesian learning model to update internal beliefs about event timings, based on the previously encountered intervals between events. From the resulting posterior distribution over intervals, we extracted two information-theoretic variables that varied from event to event: (i) entropy, a measure of uncertainty about the occurrence of the upcoming event; (ii) Shannon information, a measure of

surprise elicited by the occurrence of the event. We correlated both variables with MEG activity, across the cortical power spectrum and MEG sensors, but either before (for uncertainty) or after the event (for surprise), using cluster-based permutation statistics in space, time and frequency. Uncertainty and surprise correlated positively with trial-to-trial variations in reaction time in the button-press condition, for both target on- and offsets. Thus, both variables affected behavior. Uncertainty correlated negatively to medial centroparietal MEG power in the 8-15 Hz frequency range before target offsets. Surprise correlated negatively to power modulations after perceptual events, with peaks at around 5 Hz and 20 Hz. The distributions of these correlations were widespread and different between target on- and offsets. This correlation with surprise was not due to the duration of the preceding interval only.
We conclude that uncertainty and surprise about the timing of behaviorally relevant perceptual events shapes cortical population dynamics across widespread brain regions and frequency bands.

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Poster

713. Perceptual Decision Making

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Topic: H.02. Human Cognition and Behavior

Support: German Research Foundation (DFG), DO 1240/3-1

German Research Foundation (DFG), SFB 936/Z

National Institutes of Health (NIH), R03DC015618

Title: Phasic pupil-linked arousal reduces decision biases in mice and men

Authors: *J. W. DE GEE[1,2], K. TSETSOS[1], D. A. MCCORMICK[4], M. J. MCGINLEY[5], T. H. DONNER[1,2,3]
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Abstract: The state of the brain changes constantly, with profound consequences for cortical computation and behavior. We have recently shown that (i) pupil diameter in mice closely tracks variations in cortical state (McGinley et al, *Neuron*, 2015); and (ii) evoked pupil dilations in humans predict a reduction in perceptual choice biases (de Gee et al, *eLife*, 2017). Here, we

performed a direct comparison of the behavioral correlates of evoked pupil responses in humans and mice performing the same auditory decision task. We built on observations in both species, that rapid pupil dilations are associated with phasic responses of the noradrenergic system (Reimer et al, *Nature Comm*, 2016; de Gee et al, *eLife*, 2017).
We tracked the pupil diameter of 20 humans and 5 mice during a challenging auditory go/no-go detection task. Each trial consisted of 2-7 noise tokens (1 s duration each), with a weak signal tone (pure sine wave) superimposed onto the last noise token. Subjects had to respond to the signal, and withhold a response for pure noise sounds. Humans responded with a button press, mice by licking for sugar water reward. Errors (false alarms and misses) were followed by timeouts (8-s). We quantified the evoked pupil response for each sound in terms of the change in pupil diameter from sound onset to median reaction time. Humans also performed a yes-no (forced choice) version of the task, which entailed a single tone and a button press (for 'yes' or 'no') on each trial. We used these data to validate and compare several measures of the evoked pupil response.
Both species exhibited robust evoked pupil responses on all trial types, including misses and correct rejects (i.e., without motor response). Also in both species, task-evoked responses predicted a reduction in conservative bias (i.e., an increased tendency to respond 'yes') but no change in sensitivity. Critically, the same effect was present in the yes-no task in humans, in which motor responses were balanced across 'yes' and 'no'-choices. The bias reduction could neither be explained by pre-trial 'baseline' pupil diameter levels, nor by non-linearity of the pupil response (e.g., floor or ceiling effects).
In sum, pupil-linked, phasic arousal suppresses decision bias in humans and mice. This trial-to-trial variation of decision bias accounts for a large part of the behavioral variability, which would appear as random 'noise' without tracking arousal. We propose that pupil dilation can be used as a common reference signal that cuts across species and levels of analysis, from single neurons to complex behaviors.

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Poster

713. Perceptual Decision Making

Location: Halls A-C

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Program#/Poster#: 713.08/UU50

Topic: H.02. Human Cognition and Behavior

Title: The role of saccades and visual information quantity on spatiotemporal patterns of parietofrontal ERPs underlying the perception of complex tool-use affordances

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Abstract: Understanding the affordances of tools (i.e. how they are grasped and used) is vital for daily life. Prior research has identified the importance of parietal and frontal regions in recognizing the affordances of tools. However, parietofrontal regions are multifaceted and in particular, they underlie the control of eye movements and visuospatial attention. It is plausible that parietofrontal activity in response to viewing tools could be coupled with activity underlying attention and gaze control. Yet it is unclear how parietofrontal processing of affordances are influenced by attention and eye movements. To this end, we sought to evaluate the relationship between the two aforementioned processes via EEG and eye tracking as participants evaluated contextual and grasp-specific, static tool-use scenes in two distinct experiments. The first experiment was a flash experiment where stimuli durations were 100ms, automatically negating saccades and forcing participants to rely on extrafoveal information. In the second experiment, stimuli durations were increased to 500ms, allowing for the reemergence of saccades and foveal attention. Participants were instructed to judge whether the tool-object relationship was correct or incorrect. Response accuracies and latencies were similar in both experiments. The key result showed that the polarity, spatiotemporal patterns of parietofrontal activity and cortical source activations when evaluating the type of tool-grasp were sensitive to visual information quantity and the observer's ability to foveally parse the scene. Distinctively, parietofrontal activity when evaluating tool-use contexts were largely unaffected by gaze behavior/visual information quantity and was similar in both experiments. Results here shed new light on how eye movements and visual information specifically modulate grasp-specific parietofrontal circuits.

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Poster

713. Perceptual Decision Making

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 713.09/UU51

Topic: H.02. Human Cognition and Behavior

Support: EPSRC DOCTORAL TRAINING GRANT EP/M506539/1

Title: Changes to post-sensory processing predict performance enhancements in human multisensory decision making

Authors: *G. M. DE SOUSA[1], L. FRANZEN[1], C. KAYSER[2], M. G. PHILIASTIDES[2]
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Abstract: Real-world decisions often require the integration of congruent information across sensory modalities. Multisensory integration in perceptual decision making can improve decision accuracy compared to using unisensory information alone, however it is unclear whether behavioural improvements result from changes to early sensory or post-sensory processing. Our previous human EEG studies have identified temporally distinct components encoding early sensory evidence ('Early' component) and later decision-related evidence ('Late' component). Here we exploit these neural representations to test whether multisensory enhancements are due to early-sensory or post-sensory processing. We initially trained 31 participants on separate speeded image (face/car) and sound (speech/car) categorisation tasks. Behavioural and EEG data was then collected using visual (unisensory) and audio-visual (multisensory) interleaved trials. We used four levels of visual noise and one - subject-specific - auditory difficulty level, obtained at peri-threshold performance during training. We found increased decision accuracy but reduced reaction times during multisensory trials. As expected participant accuracy increased and reaction times decreased as visual noise in the stimuli increased. We ran a linear multivariate discriminant analysis of stimulus-locked EEG data to classify between face-vs-car trials (collapsing across trial modality). This produced a measurement of the single-trial discriminating component amplitudes of the Early and Late components we reported in earlier work, indexing sensory and decision evidence respectively. After identifying subject-specific Early and Late components (based on timing, topography and discriminator performance), we subdivided trials by modality. We found that discriminator amplitudes of our Late, but not the Early, component were significantly higher for multisensory compared to unisensory trials. Crucially, the Late component amplitude difference between unisensory and multisensory trials predicted behavioural improvements across participants. Our results suggest that the inclusion of auditory evidence provides more information leading to improved decision accuracy, and that this additional information increases the processing time but also the quality of post-sensory decision-related visual evidence. The absence of any multisensory effects during early sensory encoding in our task suggests that a near simultaneous unimodal processing of sensory evidence precedes a later post-sensory processing of multimodal evidence for combining congruent sensory information to form a decision.

Disclosures: G.M. De Sousa: None. **L. Franzen:** None. **C. Kayser:** None. **M.G. Philiastides:** None.

Poster

713. Perceptual Decision Making

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Topic: H.02. Human Cognition and Behavior

Support: EPSRC GRANT (EP/M506539/1)

Title: Temporal characterization of the neural correlates of multisensory perceptual decision making in adult dyslexia

Authors: *L. FRANZEN, G. M. DE SOUSA, C. KAYSER, M. G. PHILIASTIDES
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Abstract: Recent evidence has shown that adults with dyslexia exhibit obvious fundamental deficits spanning multiple sensory systems when performing simple integration tasks. These studies suggest that deficits start as early as the initial perceptual encoding of the evidence. Particularly, dyslexics are believed to exhibit reading impairments since this process requires the integration of congruent multisensory information across audiovisual modalities. As a consequence, these impairments can lead to hampered development of linguistic proficiency. However, it remains unclear whether dyslexic adults exhibit similar impairments when integrating audiovisual multisensory evidence in a perceptual decisions task.
Here we trained 28 dyslexics and 22 age matched controls on separate speeded image (face/car) and sound (speech/car) categorisation tasks. Behavioural and EEG data was then collected using visual (unisensory) and audiovisual (multisensory) trials. We used four levels of visual noise and one – subject-specific – auditory difficulty level, obtained at perithreshold performance during training. We found increased decision accuracy but reduced reaction times during multisensory trials for both groups, however, overall dyslexics benefited less than controls. As expected participant accuracy increased and reaction times decreased as visual noise in the stimuli decreased for both groups. Overall, dyslexics were slower than controls.
Our previous EEG work in non-dyslexics revealed temporally distinct components encoding early sensory evidence (‘Early’) and later decision-related evidence (‘Late’). Here, we exploited these components to investigate the extent to which multisensory integration affects early or later processing stages in the two groups. Specifically, we ran a linear multivariate discriminant analysis of stimulus-locked EEG data to classify between face-vs-car trials (collapsing across trial modality). This produced a measurement of the single-trial discriminating component amplitudes of the Early and Late components we reported in earlier work.
We found that while controls exhibited increased component amplitudes for the Late, but not the Early, component for multisensory compared to unisensory trials – consistent with a post-sensory influence of multisensory integration – this effect was less pronounced for dyslexics. Our neural results suggest that adult dyslexics can benefit from audiovisual integration of complex perceptual stimuli but to a lesser extend and with increased deliberation times compared to controls.

Disclosures: L. Franzen: None. **G.M. De Sousa:** None. **C. Kayser:** None. **M.G. Philiastides:** None.

Poster

713. Perceptual Decision Making

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Title: Concurrent increases in spatial stability and temporal neural dynamics during perceptual decision making

Authors: *N. A. KLOOSTERMAN[1], J. J. FAHRENFORT[2], D. D. GARRETT[1]
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Abstract: Recent work has shown that upon conscious perception, the stability of neural activity increases across cortical sites (Schurger et al., *PNAS*, 2015). Such spatial stabilization could reflect attractor dynamics that draw network activity toward a low-energy decision state. Another line of research, however, links increased moment-to-moment neural *variability* to improved cognitive processing (Garrett et al., *Neurosci Biobehav Rev*, 2013). Here, we aimed to test the intriguing possibility that brain activity can stabilize spatially around a perceptual decision, while simultaneously becoming more temporally dynamic. Specifically, we asked whether spatial neural stabilization (i) occurs either during or after a perceptual decision; (ii) whether it can be modulated by level of decision certainty, and; (iii) how the underlying temporal neural dynamics behave during spatial stabilization.
We addressed these questions by quantifying the spatial and temporal variability of the EEG of 16 human subjects reporting faint target stimuli within a stream of non-targets. Subjects completed three one-hour sessions separated by days. In different conditions, we encouraged subjects to require either low or high certainty for reporting targets by penalizing either misses or false alarms, respectively. We quantified spatial EEG variability by computing directional variance (dva), which treats each sample across electrodes as a multi-dimensional vector, and measures the directional dispersion of these vectors. We computed dva within trials using a sliding window of 100 ms. We quantified concomitant changes in temporal EEG variability using multi-scale entropy (mse) for time scales 1 (256 Hz) until 42 (time series coarse grained to ~6 Hz) (Grandy et al., *Sci Rep*, 2016). For both dva and mse, we subtracted variability in pre- from post-target stimulus intervals, focusing on transient changes in neural dynamics.
We found that spatial stability increased in high vs. low certainty conditions. In line with an intra-decisional role, this increase occurred ~0.5 s before report, but not after. Critically,

heightened spatial stabilization predicted individual differences in high versus low certainty increase (in behavior), suggesting that such stabilization reflects the level of certainty when reporting a target. Strikingly, during spatial stabilization, within-electrode temporal entropy also increased across most time scales. We conclude that the human brain appears to invoke a spatially similar, yet temporally dynamic regime during effective perceptual decision making.

Disclosures: N.A. Kloosterman: None. **J.J. Fahrenfort:** None. **D.D. Garrett:** None.

Poster

713. Perceptual Decision Making

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Program#/Poster#: 713.12/UU54

Topic: H.02. Human Cognition and Behavior

Support: NIMH Intramural Research Program

Title: The impact of sustained and dynamic uncertainty on simultaneous perceptual- and reward-based decision making

Authors: *M. GHANE[1,2], S. JAPEE[3], J. A. RICHEY[1], L. G. UNGERLEIDER[4]
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Abstract: In complex environments, individuals must determine simultaneously what objects are and what they are worth. There is growing evidence that choices are driven by optimal integration of perceptual and reward information. However, the degree to which the underlying mechanisms of decision making are domain-specific or domain-general, is not clearly understood. Differing theoretical frameworks and task designs within perceptual and reward domains make it difficult to comparably study their distinct and overlapping neural substrates. The current study aimed to test how sustained and dynamic manipulations of perceptual uncertainty (PU) and reward uncertainty (RU) impact decision making.
Participants completed two versions of a combined probabilistic reward and perceptual choice task. On each trial, participants viewed a face and a house (target stimuli) and two car images (distractor stimuli), presented in four locations around a central fixation. To manipulate PU we varied the relative phase coherence of the face and house target images (5 levels). RU was manipulated by changing the probability of receiving 8 and 2 cents for selecting either target (5 levels). Distractor images were always of low coherence and were associated with no reward. Participants were instructed to make choices that maximized reward. To test the impact of domain-specific task manipulations, in one version of the task RU was fixed within each run (varied across runs), while PU was manipulated across trials. In the second version, PU was fixed within run (varied across runs), and RU was manipulated across trials.

Average choice percentages for each stimulus type in each task revealed that individuals were less likely to select a stimulus if it was associated with high perceptual or reward uncertainty. This is consistent with evidence that perceptual and reward information is integrated to drive complex choice. Additionally, choice was not impacted by task type, suggesting that domain-specific sources of uncertainty did not uniquely contribute to behavioral effects. Instead, behavior appears to be driven by a domain-general system that reflects the overall degree of environmental uncertainty through an optimal combination of perceptual and reward information. To further test this hypothesis, we plan to collect fMRI data while subjects complete each task. We aim to use a predictive coding model to computationally define behavior and underlying neural activity. Results from these experiments will shed light on the degree of domain specificity in decision making and provide further insight into the neural mechanisms that drive complex choice behavior under varying sources of uncertainty.

Disclosures: M. Ghane: None. **S. Japee:** None. **J.A. Richey:** None. **L.G. Ungerleider:** None.

Poster

713. Perceptual Decision Making

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Program#/Poster#: 713.13/UU55

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust 091593/Z/10/Z

Title: Variability in psychopathology is linked to confidence but not performance in perceptual decision-making

Authors: *T. SEOW[1], M. ROUAULT[2], C. M. GILLAN[1], S. M. FLEMING[2]
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Abstract: Distortions in the ability to evaluate one's own behavior are associated with poor mental health. However, it remains unknown whether such shifts in self-evaluation are due to alterations in metacognition, or a downstream consequence of changes in sensory and decision processes. Using perceptual decision-making as a model system, we related parameters governing both decision formation and confidence to self-reported trans-diagnostic symptom dimensions in a large general population sample (N~1000). Variation in psychopathology was unrelated to either speed or accuracy of decision formation. In contrast, we reveal a bidirectional link between psychopathology and confidence: a symptom dimension related to anxiety and depression was associated with lower confidence, whereas a dimension characterizing intrusive thoughts was associated with higher confidence and disrupted metacognition. Our results indicate that shifts in metacognitive evaluation may represent a pervasive computational

correlate of psychiatric symptoms, creating a bridge between impaired decision-making and the emergence of common expressions of psychopathology.

Disclosures: T. Seow: None. **M. Rouault:** None. **C.M. Gillan:** None. **S.M. Fleming:** None.

Poster

713. Perceptual Decision Making

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Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust Grant 096185

Title: Neural mediators of changes of mind about perceptual decisions

Authors: *S. M. FLEMING[1], E. J. VAN DER PUTTEN[2], N. D. DAW[3]
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Abstract: Changing one's mind on the basis of new evidence is a hallmark of cognitive flexibility. To update one's confidence in a previous decision, additional evidence must be represented in a coordinate frame that tracks the accuracy, rather than the identity, of a previous choice, but how this process unfolds in the human brain remains unknown. To address this question we manipulated whether additional sensory evidence supports or negates a previous motion direction discrimination judgment while recording markers of neural activity in the human brain using fMRI. After an erroneous decision, stronger post-decision evidence led to progressively lower confidence ($P < 0.001$ for both behavioural and fMRI sessions) whereas after a correct decision, confidence was increased due to the confirmatory influence of new evidence ($P < 0.001$ for both behavioural and fMRI sessions). We used an incentive scheme in which people were paid both for being highly confident and right, and unconfident and wrong, allowing the dissociation of accuracy updates (change in P(correct|new evidence)) from changes in both evidence strength and decision value. A computational signature of accuracy update was observed in the activity of posterior medial frontal cortex (pMFC). In contrast, distinct activity profiles in lateral prefrontal cortex mediated changes in subjective confidence independently of changes in decision value. Together our findings reveal neural mediators of post-decisional changes of mind in the human brain, and indicate possible targets for ameliorating deficits in cognitive flexibility.

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Poster

713. Perceptual Decision Making

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Support: ESRC Grant ES/L012995/1

British Academy Grant SG121587

Title: Human ventromedial prefrontal cortex encodes early signatures of confidence in perceptual decisions

Authors: *S. GHERMAN, M. G. PHILIASTIDES
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Abstract: The ability to estimate the accuracy of our judgments by means of confidence is a fundamental aspect of the decision making process, and crucial to adaptive behaviour. Although recent years have seen significant advances in characterising the neural basis of confidence, its spatiotemporal dynamics during perceptual decision making remain unclear. In our previous work, using time-resolved EEG measurements, we identified early confidence-related neural signals emerging during the perceptual decision itself. Here, we aimed to extend these findings and provide a more complete spatiotemporal account of confidence, using a simultaneous EEG/fMRI approach. Specifically, we hypothesised that using the trial-to-trial variability of electrophysiologically-derived (i.e., endogenous) measures of confidence to detect associated fMRI responses would provide a more accurate and temporally precise spatial representation of the confidence signals around the time of decision, than would be possible by relying on behavioural confidence ratings and fMRI measurements alone.
To this end, we collected simultaneous EEG/fMRI data from 64 scalp electrodes inside a 3T MRI scanner while participants (N=24) performed a random-dot direction discrimination task and gave confidence ratings on each trial. Motion coherence was held constant across trials to control for confounding effects of task difficulty. Using a multivariate single-trial classifier to discriminate between High vs. Low confidence trials in the EEG data, we extracted an early, stimulus- and accuracy-independent discriminant component appearing prior to participants' behavioural response. By regressing the resultant single-trial component amplitudes against the fMRI response, we identified a positive correlation with this early confidence signal in a region of the ventromedial prefrontal cortex (vmPFC), which has previously been linked mainly with value-based decisions. Importantly, this activation was additional to what could be explained by subjects' confidence ratings, as well as other potential confounds (task performance, response time, attention) included in the same model as regressors of no interest. Furthermore, a functional connectivity analysis revealed a confidence-modulated link between the activation in

the vmPFC and the right rostrolateral prefrontal cortex, a region known to be implicated in metacognitive evaluation. Our results suggest that the vmPFC may support an early confidence signal which precedes and potentially informs metacognitive evaluation, and are in line with recent work proposing a domain-general role for this region in encoding confidence.

Disclosures: S. Gherman: None. **M.G. Philiastides:** None.

Poster

714. Social and Emotional Processes

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Topic: H.02. Human Cognition and Behavior

Support: The Hector Foundation

Title: Neurocognitive processing in breast cancer patients: Harmful effects of messages perceived as a threat

Authors: *A. N. SOKOLOV[1], M. A. PAVLOVA[3], S. Y. BRUCKER[1], D. WALLWIENER[2], E. SIMOES[1]
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Abstract: Breast cancer is the most common type of cancer among women. In gynecologic oncology, much negative health-related information is communicated to patients. When diagnosed with breast cancer, women are faced a lot of threatening information that may substantially hinder their cognitive abilities and decision making (e.g., during informed consent) and, eventually, result in gender-specific (and often suboptimal) coping with the disease. Previous work demonstrated gender specific influence of information delivery: Negative gender-related messages such as “men are usually better than women on a task” drastically reduce performance on a visual cognition task (without any initial gender gap documented), with a much stronger effect in women (e.g., Pavlova et al., 2014). This reduction is even greater in breast cancer patients. There are also indications on the gender-related effects of negative messages on brain activation in healthy participants. In this ongoing project, we intend to clarify whether in breast cancer patients, gender-related negative messages affect brain activation during performance of demanding cognitive tasks. Should the hypothesis hold true, this would suggest that negative information can block coping-related brain processes. We examined performance on a visual cognition task in two groups of mastocarcinoma patients (age, 40 - 55 years; with/without negative messages such as above) and two control groups of matched healthy women. With negative messages, patients scored lower than controls, and lower than patients

without negative messages, indicating effects of both disease and message. Remarkably, the lowest scores occurred in patients with negative messages. Future research will uncover brain mechanisms of these effects in breast cancer patients. The outcome shows for the first time the impact of disease and information on visual social cognition, presumably blocking visual cognitive processing. This helps to clarify the neurocognitive effects of information delivery in gynecologic oncology and oncology at large.

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Poster

714. Social and Emotional Processes

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 714.02/UU59

Topic: H.02. Human Cognition and Behavior

Support: BUILD PODER

Title: Differences of n170 amplitudes in emotion information processing among individuals with alexithymia

Authors: *D. A. BANUELOS, K. GARCIA, K. JOHNS, S.-M. KANG
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Abstract: Few studies have explored how individuals with alexithymia process emotional information using Event-Related Potential (ERP). Pollatos and Gramann's study (2011) demonstrated that individuals with high degrees of alexithymia (HDA) show an early processing deficit compared to individuals with low degrees of alexithymia (LDA) by focusing on P100 and P300 peaks. However, their study did not explore differences in the amplitude of N170. Literature has shown that N170 marks the point in processing when a visual stimulus is consciously interpreted as a face and its occurrence depends on our past experience of what is a 'face' (Rossion 2014). The main purpose of the current study was to further explore differences in N170 amplitudes between individuals with HDA and LDA, when they process facial expressions.
From a pool of 1576 college students, 26 were selected based upon their score on the Toronto Alexithymia Scale (Bagby et al., 1994). Of the 26 selected, data from 14 participants (7 high and 7 low) was usable. In an individual session, a total of 11 electrodes were manually placed on a participant's head (PZ, CZ, and FZ) and face using the 10-20 international system. Each participant was asked to identify six facial expressions (angry, disgusted, fearful, happy, sad, and surprised) presented on a computer screen. A total of 42 faces taken from the NimStim Face Stimulus Set (Tottenham et al., 2002) were used in either a whole face or half face condition. In

the half face condition, either the top or bottom half of the face was randomly removed.
The results of the current study revealed that the mean amplitudes of N170 between high and low alexithymia conditions were marginally different from each other, F (1,12) = 3.74, p = .077. The average N170 amplitude of the LDA group (M = -4.48, SE = .84) was higher than that of the HDA group (M = -2.18, SE = .84). More importantly, however, there was the significant 3-way interaction effect of face (whole vs. half) x condition (HDA vs. LDA) x locations (PZ, CZ, and FZ), F (2, 24) = 13.25, p = .000. The individuals with HDA tended to use less cognitive effort to configure emotion expressions on the whole faces, whereas they put more effort for the half faces. In contrast, the individuals with LDA seemed to put similar levels of effort for both the whole and half faces. However, the highest N170 amplitude appeared on the different sites depending on the face conditions - the CZ site for the whole faces and the PZ site for the half faces, respectively. The significance and implications of the current findings were discussed.

Disclosures: **D.A. Banuelos:** None. **K. Garcia:** None. **K. Johns:** None. **S. Kang:** None.

Poster

714. Social and Emotional Processes

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Support: ANII POS_NAC_2015_1_109714

CSIC ID 364

Title: Evoked potentials of social comparisons in people with social anxiety/depression

Authors: *V. PAZ, E. NICOLAISEN-SOBESKY, G. FERNANDEZ-THEODULOZ, S. GARAT, O. NIEVAS, A. PÉREZ, D. KESSEL, Á. CABANA, V. B. GRADIN
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Abstract: Social anxiety and depression are disabling disorders that significantly impact on the interpersonal functioning of individuals. Despite the importance of social difficulties in these disorders, little is known about the neural substrates underlying such difficulties.
In an ongoing study we are measuring *event related potentials* (ERPs) in unmedicated socially anxious and/or depressed participants (n=28) and matched healthy controls (n=23). During the study, participants view their own and a co-player´s gain and loss outcomes based on their performance in a time estimation task. There are four types of outcomes: participant correct/co-player incorrect, participant incorrect/co-player correct, both correct and both incorrect.
Results showed that socially anxious/depressed participants reported significantly more anger, sadness, nervousness, guilt, shame and disappointment and less happiness in response to the task

than controls. Socially anxious/depressed participants also reported more shame for all the outcomes except "both correct", more disappointment for the outcome participant incorrect/co-player correct, more shame and nervousness about discussing the outcomes with their co-player, and having the perception that they played worse, compared with controls.
ERPs results showed an effect of outcome with negative outcomes (in which at least one player had a negative outcome) eliciting a enhanced Medial Frontal Negativity (MFN) peaking around 220-320 ms at fronto-central electrodes compared with the "both correct" outcome. There was no significant effect of group or a group*outcome interaction.
Results indicate an accentuated negative emotional response in socially anxious/depressed individuals to social comparison situations. The ERPs results are in agreement with previous studies reporting that the MFN is modulated by losses vs. gains monetary rewards and positive vs. negative social outcomes. Our results indicate that the MFN, a component that has been related to the motivational/affective impact of outcomes, is modulated by social comparison outcomes. The lack of significance of the group or the group*outcome interaction effects regarding ERP results may be due to sample limitations as recruitment is still ongoing. Once completed, this study may contribute to understand how socially anxious/depressed people process social comparisons.

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Poster

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Topic: H.02. Human Cognition and Behavior

Support: Brain/MINDS, AMED

Title: Reduced modulation of the language-related network during perception of acoustically degraded speech in autism spectrum disorder

Authors: *R.-I. HASHIMOTO[1,2], T. ITAHASHI[2], M. NAKAMURA[2], H. OHTA[2], C. KANAI[2], N. KATO[2]
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Abstract: Individuals with autism spectrum disorder (ASD) are known to be often highly sensitive to acoustic disturbances for perception of speech sounds, which makes speech communication in everyday life difficult. However, neural mechanisms underlying such speech

perception difficulty have not been clarified in the ASD brain. Past neuroimaging studies for neurotypical individuals have shown that speech perception under acoustically degraded conditions involves the speech motor cortex, which may reflect top-down control processes on activity in speech perception areas. Therefore, it is possible that speech perception difficulty in ASD may stem from reduced load-dependent changes in functional connectivity (FC) between speech motor and perception areas.
In order to test this hypothesis, we designed a speech perception task, which consisted of three conditions that were different either in levels of acoustic degradation or speech intelligibility as follows: (1) clear speech (CS), (2) 8-channel vocoded speech (VCS), and (3) 8-channel vocoded speech with spectral rotation (VSR). 21 adult males with high-functioning ASD and 24 matched typically-developed (TD) males participated in this study. MRI signals were recorded using a 3T Siemens MRI scanner (TR = 2.5 sec, 40 axial slices, spatial resolution = 3.3 x 3.3 x 4 mm, 250 volumes). We used SPM 8 for data preprocessing and statistics. Analysis of FC was performed by generalized psychophysiological interaction (gPPI) analysis. Effects of acoustic degradation were estimated for both brain activation and FC by a contrast of [VCS vs. (CS + VSR)].
First, the acoustic degradation effect on activation was compared between ASD and TD. The contrast revealed multiple significant clusters of activation in regions related to attention and speech motor control, including bilateral anterior cingulate cortex, insular cortex, inferior frontal cortex, and premotor cortex. Second, the gPPI analysis seeding the left dorsal premotor cortex showed that the acoustic degradation effect on FC was significantly reduced in the left temporo-parietal junction. Simple regression analysis using the scores of autism quotient (AQ) revealed that reduced FC was significantly associated with the severities of autistic trait among individuals with ASD. These observations support the hypothesis that FC between speech motor and perception areas is less modulated depending on levels of acoustic degradation in the ASD brain.

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Poster

714. Social and Emotional Processes

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Topic: H.02. Human Cognition and Behavior

Support: 31Z20130012945

Title: Late positive event-related potentials in electroencephalography can distinguish acquaintances from strangers when both groups recognize faces

Authors: *S. LEE, J.-H. KANG, I. OAKLEY, S.-P. KIM
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Abstract: Recognition of a familiar face can be important for not only basic cognitive neuroscience but also advanced personal authentication schemes. When a person looks at faces, social and emotional aspects as well as appearance are processed in the brain, which can induce different cognitive processes between genuine users and imposters. For the development of such an authentication scheme, we proposed a new authentication paradigm using familiar faces together with electroencephalography (EEG) and compared neural activity between acquaintances and strangers while they searched for known faces via an event-related potential (ERP) analysis. 28 pictures of human faces were prepared among which 4 were designated as target faces. 29 participants belonged to one of 2 groups: the acquaintance group of 14 participants indeed knew 4 target faces for long time (> 1 years) whereas the stranger group of 15 participants had not known a priori any face but were informed of 4 target faces before the task. In each trial, participants were shown 8 faces arranged in the form of a 3x3 matrix with the center slot empty. The face matrix was presented for different durations of 1, 1.5, 2 or 2.5 s over four blocks. Half of trials in each block included a target face (i.e. familiar condition) and the rest did not (i.e. unfamiliar condition). Participants searched for a target face and located it in the matrix using a numerical keypad (3x3 matrix for of 9 keys). If they could not find the target, they pressed the center key on the keypad. EEG and eye tracking data were recorded simultaneously. The epochs for ERP analysis were time-locked to the onset of the longest fixation on correct answer in the familiar condition or the average response time of the familiar condition in the unfamiliar condition. Error rates were similar between two groups ($p > 0.05$). The block with 1s stimulus duration yielded a significantly higher error rate than others ($p < 0.001$). The ERP analysis revealed that late positive potentials (LPPs) at FC1 and F3 were significantly larger in the acquaintance group than in the stranger group ($p < 0.05$) even when the both groups successfully identified the target faces. This is in line with preceding studies showing that LPP reflects more elaborate processing such as long-term memory traces. The current study suggests plausibility of our new paradigm as a novel authenticating scheme using EEG and face recognition.

Disclosures: S. Lee: None. **J. Kang:** None. **I. Oakley:** None. **S. Kim:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

Support: Istituto Italiano di Tecnologia

Title: Anatomical evidence of the insula connections with the mirror system in humans and macaque monkeys

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Abstract: Actions can be performed with different vitality forms (e.g. in a gentle or rude way). In previous fMRI studies, we demonstrated that both observation and imagination of arm actions vitality forms are encoded in the left dorso-central insula. It appears therefore that this sector of the insula has a fundamental role in expressing our own vitality forms and in recognizing those of others. In the present study, we investigated whether the dorso-central insula is connected with the fronto-parietal nodes of the action recognition circuit in humans and monkeys. To this purpose, in humans, we used a combination of functional (Psycho-Physiological Interaction, PPI) and anatomical connectivity (Diffusion Tensor Imaging, DTI). To define the seeds of the interest for DTI, we carried out the PPI analysis on functional data showing that the anterior intraparietal sulcus and the inferior frontal gyrus are functionally connected with the dorso-central insula. An additional seed was placed in the ventral premotor cortex activated during action observation. DTI results highlighted that, in humans, the dorso-central insula is connected with both the seeds of the parietal and premotor cortex as well as with that of the inferior frontal gyrus. To assess a correspondence between the human circuit and that previously described by tract tracing studies in the monkey, we performed a DTI study, in the monkey, by placing the seeds of interest in the premotor and parietal mirror circuit nodes, and in the ventro-lateral prefrontal cortex (VLPFC), recently described to be activated during action observation. A further seed was placed in the dorso-central insula. The results showed that, as in humans, the monkey dorso-central insula is connected with the parietal and premotor mirror circuit nodes as well as with the VLPFC. Altogether, our results demonstrate that the dorso-central insula is connected with the parieto-frontal mirror network suggesting that this insular sector may modulate this circuit during vitality form perception and expression.

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Poster

714. Social and Emotional Processes

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 714.07/UU64

Topic: H.02. Human Cognition and Behavior

Title: Brain signal complexity during social perception in infancy is associated with epigenetic variability of the oxytocinergic system

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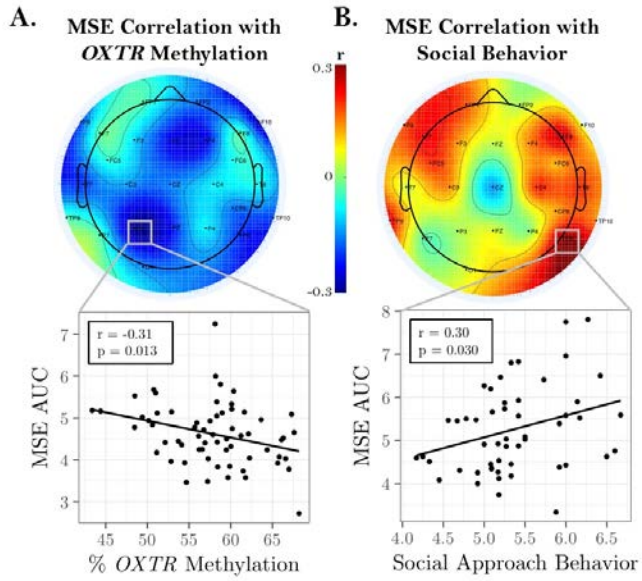
Abstract: Measures of neural complexity capture the inherently fluctuating nature of the brain and are positively associated with cognitive development and behavioral performance. Oxytocin, a naturally occurring neuromodulator, regulates both social behavior and brain signaling. Individual differences in the endogenous oxytocinergic system are in part due to epigenetic variability of the oxytocin receptor (*OXTR*) through DNA methylation. We have previously identified a region of *OXTR* in which increased methylation is associated with decreased levels of transcription in human cortex. Therefore, those with low methylation likely have increased access to endogenous oxytocin. Methylation at this site shows significant variability in the population, is elevated in individuals with autism, is associated with differences in brain function and connectivity in healthy adults, and can be assessed from peripheral tissue. We hypothesized that early life differences in the oxytocinergic system drive differences in neural complexity during social perception. To test this hypothesis, we assayed *OXTR* methylation from 101 infants at 5 months of age. At 8 months of age, we presented the same infants with social auditory stimuli while undergoing EEG, and collected measures of infant social behavior. Neural complexity was quantified as the area under the multiscale entropy curve (MSE AUC). We find that infants with decreased *OXTR* methylation, or higher access to endogenous oxytocin at 5 months of age, show significantly increased neural complexity in response to social stimuli at 8 months of age. Infants with increased neural complexity also show significantly increased approach behavior at 8 months of age. These results suggest that the oxytocinergic system may impact social behaviors by establishing unique neural patterns to social stimuli early in life.



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Poster

714. Social and Emotional Processes

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Program#/Poster#: 714.08/UU65

Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number 16H01479

Kumon Institute of Education Co., Ltd

Title: Neural correlates of deceptive behavior in children with autism spectrum disorder

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Abstract: Introduction: Deception is a psychological process by which one individual deliberately attempts to convince another to accept as true what the first individual knows to be false. To deceive other person requires inhibition of true response and production of deceptive one. Successful deception involves anticipating responses and inferring what another person knows, especially in social contexts. Previous studies have revealed the difficulty and developmental delay in deception and executive dysfunction in children with autism spectrum disorder (ASD). However neurocognitive traits of ASD are poorly understood. In this study, we investigated neural correlates of deceptive behavior in children with ASD, using functional magnetic resonance imaging.
Methods: Twelve children with ASD and 14 typically developing (TD) children, aged 6 to 12-year old, participated in this study. The diagnoses of all children with ASD were confirmed using Autism Diagnostic Interview-Revised. Parent of participants answered Autism Quotient (AQ; Wakabayashi et al, 2007) about their child. Participants were scanned while performing interactive games involving deception. 1 interactive game trial took 19-seconds, and there were 64 trials in total. Trials were pseudo-randomly presented with average 4-seconds inter stimulus interval. The hemodynamic response for each event was modeled from the onset of the appearance of the question. Imaging analyses were conducted using SPM 8. This study was approved by the Institutional Review Board of the Tohoku University. As per the Declaration of Helsinki, after we had explained the purpose
and procedures of the study, written informed consent was obtained from each subject and a parent prior to MRI scanning.
Results: We found that the activation in the right inferior parietal lobule was marginally significantly different between groups and conditions. In ASD group, the activation of this

region was higher than TD group in the deception condition (MNI coordinates (42,-30, 46); uncorrected P < .001 at voxel level, FWE corrected P < .10 at cluster level). We also found that the activations of right anterior cingulate cortex (ACC) and anterior insula is significantly positively correlated with AQ score in the deception condition only in ASD group (uncorrected P<.001 at voxel level, FWE corrected P<.05 at cluster level).
Discussion: The inferior parietal lobule is the part of inhibition network (Lee et al., 2002). ACC and insula are also related with response inhibition. Especially, insula activation is correlated with costs of inhibition. Therefore these regions play a key role for making successful deception in children with ASD.

Disclosures: S. Yokota: None. **T. Hashimoto:** None. **R. Kawashima:** None.

Poster

714. Social and Emotional Processes

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Program#/Poster#: 714.09/UU66

Topic: H.02. Human Cognition and Behavior

Support: Israel Science foundation

The Henry Crown Institute of Business Research

Title: A behavioral and neural study of deception

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Abstract: Deception plays a big part in social interactions, from mundane white lies up to multimillion dollar frauds. While from a utilitarian stand-point, people should lie whenever they can benefit from it, in reality this is not the case. For example, studies showed that people incorporate into their decision process the consequences of their lie on others. In this study, our objective was to identify the internal motivations that contribute to the decision to deceive another person, and outline the neural correlates of dishonest behavior. We used a task called *The Message Game*, in which a subject (Sender) sends out either a profitable yet deceptive message or a truthful but not-as-profitable message to another participant (Receiver). Payoffs varied across trials, in order to assess individual sensitivity to different motivations for deception. We defined three such potential motivations: Self Interest, Regard for Other, and Inequality.
Thirty-three subjects completed the task, while their neural activity was recorded using an fMRI scanner. Behaviorally, we found that on average participants sent a deceitful message on half the

trials. However, this behavior varied dramatically between subjects, and while some lied on nearly every single trial, others scarcely did so. Further subject-level analyses revealed high variability in motivations as well, both in *which* motivations drive the behavior and *to what extent*. On the neural level, we observed several regions implicated in the decision to deceive, including the superior temporal sulcus, posterior cingulate cortex and the temporoparietal junction (TPJ). Interestingly, we were able to identify motivation-specific regions of activations, modulated by how these motivations affects individual subjects' behavior. We found utilitarian motivations to correlate with activity in several regions, including ventral striatum and amygdala. Subjects with more other-oriented motivations showed activity in regions including the TPJ and the inferior frontal gyrus. Finally, we show that the connectivity between these social and utilitarian regions is associated with subjects' behavior.
Our results suggest that different people have different motivations to act honestly. Importantly, these differences may be traced to specific neural structures and connections.

Disclosures: A. Shuster: None. **D.J. Levy:** None.

Poster

714. Social and Emotional Processes

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01MH107513

Title: Beta wave oscillations distinguish between dynamic actions of initiating and terminating eye contact with a real partner

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Abstract: Eye contact is a universal social cue that signals intent to communicate. The intention depends upon whether one person's eyes are moving toward the observer (initiating) or away from the observer (terminating) communication. We hypothesize that neural activity during eye-to-eye interaction between an observer and a partner will differentiate between conditions where the trajectory of eye movement is either toward or away from the observer. Specifically, we compared separate frequency bands of electroencephalographic (EEG) signals acquired during dynamic eye contact events. We recorded EEG signals from pairs of participants simultaneously (13 dyads, 26 total participants) for the following two types of dynamic eye contact: 1) "toward", in which one participant ("partner") makes eye contact with an observing participant

("observer"), or 2) "away", in which the partner diverts eye gaze away from the observer. Participant dyads were positioned 140 cm across a table from each other. The two participants alternated between observer and partner trials. In each trial, the observer's gaze was directed straight ahead. The partner's gaze, instructed by an auditory cue that was not heard by the observer, randomly alternated either toward or away (10 deg) from eye-to-eye contact with the observer. The duration of each trial alternated between 1.5 and 2.5 s. EEG signals were acquired at F3, F4, F7, F8, C5, C6, PO7, and PO8 in accordance with the 10-20 standard layout. Signals were decomposed into gamma (40-100 Hz), beta (12-40 Hz), alpha (8-12 Hz), theta (4-8 Hz), and delta (0-4 Hz) frequency bands. Event types "toward" and "away" were compared for each of the frequency bands. The phase of the beta waves between 735-785 ms differed between the "toward" and "away" condition for right hemisphere DLPFC (F8 electrode, $p < 0.013$). These findings suggest that opposite intentions to communicate, signaled by dynamic eye-to-eye contact either away or toward an observer, are represented by a specific beta wave neural signature and provide a foundation for models of communication intentions in real social conditions.

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Poster

714. Social and Emotional Processes

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Program#/Poster#: 714.11/UU68

Topic: H.02. Human Cognition and Behavior

Title: Affective and cooperative interactions modulate brain connectivity within the action observation system

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Abstract: Decoding the meaning of others' actions, a crucial step for social cognition, involves different neural mechanisms. In particular, the respective contribution of the "mirror" and "mentalizing" systems to intention understanding is debated. Processing social interactions recruits both neural systems, with a different weight depending on cues emphasizing either shared action goals or shared mental states. We have previously shown that observing cooperative vs. affective social interactions elicits stronger activity in, respectively, the key-

nodes of the mirror (left posterior superior temporal sulcus (pSTS), posterior parietal (PPC) and premotor cortex (PMC)), or the hubs of the mentalizing (ventromedial prefrontal cortex (vmPFC)) systems. Here we aim at unveiling their neural dynamics by means of dynamic causal modeling in 36 healthy human subjects. We investigated the causal organization underlying the observation of human interactions expressing increasing cooperativity (involving left pSTS, PPC and PMC) vs. affectivity (vmPFC). We first explored the fixed connectivity between these regions and then assessed how increasing levels of perceived affectivity vs. cooperativity, as well as the observer's empathic aptitude, can modulate the direction and strength of their effective connections.We found very strong evidence for a neural model including the pSTS as gateway for both the observed interactions and the degree of their affectivity. The extrinsic connectivity of this input node is subject to oppositely valenced modulations by cooperativity and affectivity, promoting, respectively, reciprocal excitatory connectivity with PPC (mainly forward) and vmPFC (mainly backward). For a subset of effective connections, the strength of modulation displayed an inverse relationship with the subject's empathic aptitude. Empathy scores were negatively related to the strength of the modulation exerted by a) cooperativity on the connections from both PPC and pSTS to PMC, and b) affectivity on the connection from pSTS to vmPFC. Such a negative relationship may indicate that empathy is down-regulated by the early segregation of neural processing by the mirror and mentalizing systems.Consistent with *f*MRI data, such divergent effective connectivity suggests that different dimensions underlying the processing of social interactions recruit distinct, although strongly interconnected, neural pathways associated with the bottom-up visuomotor processing of motor intentions and the top-down attribution of affective and mental states.

Disclosures: S.F. Cappa: None. **M. Arioli:** None. **E. Catricalà:** None. **D. Perani:** None. **A.M. Proverbio:** None. **A. Zani:** None. **A. Falini:** None. **N. Canessa:** None.

Poster

714. Social and Emotional Processes

Location: Halls A-C

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Program#/Poster#: 714.12/UU69

Topic: G.03. Emotion

Support: Wheaton College G.W. Aldeen Memorial Fund

Title: Effects of acute aerobic exercise on ocular measures of emotion processing during an emotional face perception task

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Abstract: *Background*: Mechanisms of exercise-induced mood enhancement are not well understood. Given the relationship between mood and emotion, adaptive changes in attentional biases to emotional stimuli plausibly could explain exercise effects on mood. *Objectives*: To examine the effects of acute aerobic exercise and/or quiet rest on eye-tracking metrics while viewing emotional facial stimuli. *Methods*: N=35 (18 women) aged 21.1±1.4y completed two counterbalanced 30-min conditions: vigorous running or seated rest. Eye-tracking occurred pre- and 20-min post-condition. Corneal reflection was measured using a Tobii x120 sampling at 120Hz.Participants viewed 45 photographs from NimStim depicting positive (n=15), neutral (n=15), and negative (n=15) facial expressions. Number of fixations, scan path length, fixation duration, and longest fixation were analyzed using 2 Condition (control/exercise) X 2 Time (pre/post) X 3 Emotion (positive/neutral/negative) repeated measures ANOVAs. Significant interactions were decomposed using Bonferroni-adjusted pairwise comparisons. *Results*: Scan path was significantly longer for negative compared to positive images in the exercise condition (condition X emotion ($F_{(1.58,50.67)}$=4.15, p<0.03), mean difference=-46.33, p≤0.008). Fixation duration was significantly longer for positive compared to neutral images at pre-condition (time X emotion ($F_{(2,64)}$=3.21, p<0.05), mean difference=50.64, p≤0.01) and non-significantly longer compared to negative images at post-condition (mean difference=37.06, p>0.08). Compared to neutral images, positive images resulted in a significantly longer longest fixation at pre-condition (time X emotion ($F_{(2,64)}$=3.12, p≤0.05), mean difference=57.04, p≤0.004). *Discussion*: Acute exercise did not significantly alter emotional response as indexed by fixation duration, fixations, or longest fixation. Eye-tracking effectively detected different emotional processing patterns and scanning strategies while viewing emotional stimuli. Significantly longer fixation durations and longest fixation for positive images at pre-condition suggests that participants preferentially fixated on positive images even prior to any intervention. Interestingly, longer scan paths for negative images indicated hyperscanning, suggesting that participants more actively avoided fixating on any relevant aspect of negative images. Further analyses to examine defined eye and mouth areas in images and pupil dilation (cognitive load) are forthcoming.

Disclosures: C. Reyes: None. **N. Thom:** None. **H. Thomas:** None. **N. Varberg:** None. **M.P. Herring:** None. **M.J. Campbell:** None.

Poster

714. Social and Emotional Processes

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Topic: H.02. Human Cognition and Behavior

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the Ministry of Science, Research and Arts of Baden-Württemberg, Germany (grant No. 32-771-8-1504.12/1/1 to KS

Title: Spatial and temporal dynamics of the networks for body motion processing

Authors: *M. PAVLOVA[1], M. ERB[2], G. HAGBERG[1], J. LOUREIRO[2], A. N. SOKOLOV[4], K. SCHEFFLER[3]
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Abstract: Body motion delivers a wealth of socially relevant information. Yet display inversion severely impedes biological motion (BM) processing. It is largely unknown how the brain circuits for BM are affected by display inversion. As upright and upside-down point-light BM displays are similar, we addressed this issue by using ultra-high-field functional MRI (at 9.4 tesla) providing for high sensitivity and spatial resolution. Whole-brain analysis along with exploration of the temporal dynamics of the BOLD response reveals that in the left hemisphere, inverted BM activates anterior networks engaged in decision making and cognitive control, whereas readily recognizable upright BM activates posterior areas solely. In the right hemisphere, multiple networks are activated in response to upright BM as compared to scarce activation to inversion. With identical visual input with display inversion, a large-scale network in the right hemisphere is detected in perceivers who do not constantly interpret displays as shown the 'wrong way up'. For the first time, we uncover (i) (multi)functional involvement of each region in the networks underpinning BM processing, and (ii) large-scale ensembles of regions playing in unison with distinct dynamics. The outcome sheds light on the neural circuits underlying BM processing as an essential part of the social brain.

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Poster

714. Social and Emotional Processes

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Program#/Poster#: 714.14/UU71

Topic: H.02. Human Cognition and Behavior

Support: Fondation Bertarelli

Title: Neural sources and underlying mechanisms of neural responses to heartbeats, and their role in bodily self-consciousness: An intracranial EEG study

Authors: *H. PARK[1], F. BERNASCONI[1], R. SALOMON[2], C. TALLON-BAUDRY[3], L. SPINELLI[4], M. SEECK[4], K. SCHALLER[4], O. BLANKE[1]
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Abstract: Recent research has shown that heartbeat-evoked potentials (HEPs), brain activity in response to heartbeats, are a useful neural measure for investigating the functional role of brain-body interactions in cognitive processes including self-consciousness. However, the basic properties of HEPs are not yet well understood. In two experiments, using intracranial EEG, we investigated 1) the neural sources of HEPs, 2) the underlying mechanisms for HEP generation, and 3) the functional role of HEPs in bodily self-consciousness. In Experiment-1, we recorded ECG and resting state intracranial EEG data from 599 depth electrodes in 8 epilepsy patients and computed HEPs by averaging intracranial EEG data time-locked to the ECG R-peaks. Inter-trial coherence analysis of HEPs revealed that shortly after the heartbeat onset, phase distributions across single trials were significantly concentrated in 10% of the recording sites (permutation test complemented with the FDR correction, $p < 0.05$) mainly in the insula and the operculum, but also in other regions including the amygdala and fronto-temporal cortex. Such phase concentration was not accompanied by increased spectral power (FDR corrected $p > 0.05$), and did not correlate with spectral power changes (Pearson's $r = 0.057$, $p = 0.22$), suggesting that a phase resetting, rather than an additive 'evoked potential' mechanism, underlies HEP generation. In Experiment-2, we further aimed to anatomically refine previous scalp EEG data that linked HEPs with bodily self-consciousness. For that we recruited 4 epilepsy patients implanted with depth electrodes involving the insula or the operculum and recorded ECG and intracranial EEG data while the patients were performing the full-body illusion (FBI) paradigm to experimentally alter the state of bodily self-consciousness (e.g., self-identification). We found that HEP modulations in the insula reflected an experimentally induced altered sense of self-identification in two epilepsy patients (cluster based permutation test, $p < 0.05$). Such differential HEP modulation was not observed in two other patients who reported no changes in self-identification during the FBI task ($p > 0.05$), supporting our hypothesis that differential modulations of HEPs in the insula are associated with modulations of self-identification. Collectively, these results provide novel and solid electrophysiological evidence on the neural sources and underlying mechanisms of HEPs, and their functional role in self-consciousness.

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Poster

714. Social and Emotional Processes

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Program#/Poster#: 714.15/UU72

Topic: H.02. Human Cognition and Behavior

Support: MH059299

Title: Assessing effective connectivity of frontal-thalamic network interactions between OCD patients & healthy controls during basic motor control

Authors: *J. JAVED[1], *J. JAVED[1], V. A. DIWADKAR[3], A. CHOWDURY[2], P. EASTER[2], D. ROSENBERG[4], G. HANNA[5], P. ARNOLD[6]
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Abstract: Introduction
Individuals with obsessive-compulsive disorder (OCD) can be characterized by uncontrollable reoccurring thoughts (obsessions) and subsequently behaviors based on these thoughts (compulsions). These differences in thoughts and behaviors may be associated with abnormal brain network function (Diwadkar et al., 2015) and basic motor paradigms involving visually guided finger tapping eloquently evoke disordered cortical thalamic interactions (Friedman et al., 2017). Here we probed the effective connectivity of cortical-thalamic brain networks during a basic visuo-motor integration paradigm (Diwadkar et al., 2017). Dynamic causal modeling (DCM; Friston et al., 2003) was applied to fMRI signals acquired while subjects performed a basic finger tapping task under variable demands. Endogenous connections between the dorsal anterior cingulate (dACC), the supplementary motor area (SMA), the primary motor cortex (M1) and the thalamus (Thal) were investigated as was their modulation by task.
Methods
Data from twenty participants (10 healthy controls and 10 OCD children; $8 \leq \text{Age} \leq 13$) were analyzed. fMRI data (Siemens Verio 3.0T) were collected using a previously employed finger tapping paradigm with variable demands (Friedman et al., 2017). The two test conditions (periodic vs random) were differentiated by creating a different contrast vector for each. 36 competing models were created. The configuration of these models were based off the connections of interest, with two being intrinsic (SMA to M1 and dACC to SMA) and two being non-endogenous (dACC to thalamus and dACC to M1). Bayesian Model Averaging (BMA)(Penny et al., 2010) was used in to estimate connectivity parameters weighted by Bayesian posteriors.
Results
In our analysis, the likeliest generative models were not characterized by contextual modulation, and parameter estimates suggested that OCD were characterized by greater SMA to M1 endogenous connectivity.
Conclusion
These preliminary results imply that effective connectivity of motor pathways is not contextually modulated by basic motor processing. We are evaluating the specificity of these results, and their consistency with other network methods.

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Poster

714. Social and Emotional Processes

Location: Halls A-C

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Program#/Poster#: 714.16/UU73

Topic: H.02. Human Cognition and Behavior

Title: Impulsive behaviour of ADHD probands may result from biased maternal transmission of DAT and COMT gene variants

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Abstract: BACKGROUND: Attention Deficit Hyperactivity Disorder (ADHD), a common childhood onset neurobehavioral disorder, is speculated to be caused by dopaminergic dysregulation. Impulsive actions and uncontrolled behaviour are the hallmarks of ADHD probands and higher occurrence in the male subjects makes it more challenging. The Dopamine Transporter (DAT) and Catechol-O-Methyltransferase (COMT), both aiding in synaptic dopamine clearance, control neural transmission, post-receptor modulation, and plasticity. We investigated the role of functional DAT and COMT gene variants in ADHD associated impulsivity and behavioural problem. **METHOD**: Nuclear families with ADHD probands (N=217) were recruited following the DSM-IV criteria, while 260 healthy volunteers were recruited based on their academic and social achievements. Peripheral blood was collected from the participants after obtaining informed written consent. Traits were assessed through Conner's rating scale for ADHD and Tsukuyama rating scale for domain specific impulsivity. Genomic DNA isolated was used for PCR based amplification of target sites followed by DNA sequence analysis. Data obtained was analyzed by population as well as family-based methods. **RESULT**: Both impulsivity and oppositional behaviour showed positive correlation with age. Quantitative trait analysis revealed influence of rs2254408, rs2981359, rs227094, rs2254408, rs28382221, rs2981359, rs2239393 on impulsivity while rs4633 exhibited effect on oppositional trait ($P<=0.05$). rs2270913 showed significant over presence in the male probands ($P=0.04$) and biased transmission from younger mothers. Allelic and haplotypic transmission bias were noticed for rs13189021, rs28382221 and rs4633-rs2239393 ($P<0.05$). **CONCLUSION**: The study revealed association of novel gene variants with ADHD endophenotypes. Biased transmission of gene variants indicates maternal contribution in ADHD associated traits. It can be inferred that instability in synaptic dopamine clearance, as predicted by the functional role of the variants,

lead to altered dopamine level culminating in a plethora of distorted cortical stimulation which may enhance ADHD related impulsivity and oppositional trait.

Disclosures: S. Maitra: None. **S. Sinha:** None. **K. Mukhopadhyay:** None.

Poster

714. Social and Emotional Processes

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 714.17/UU74

Topic: H.02. Human Cognition and Behavior

Support: Swiss National Foundation

Title: Ongoing neuronal activity as marker of human amygdala function

Authors: *T. FEDELE[1], B. STEIGER[3], A. TZOVARA[4,5], D. BACH[4], P. HILFIKER[3], T. GRUNWALD[3], L. STIEGLITZ[2], H. JOKEIT[3,6], J. SARNTHEIN[1,6]
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Abstract: Introduction: Aversive visual stimulation elicits neuronal responses in the human amygdala but a comprehensive understanding of the underlying electrophysiology is still lacking. **Methods:** We recorded intracranial electroencephalography (iEEG) from mesial temporal electrodes in 9 patients with epilepsy who viewed eight dynamic sequences of fearful faces (aversive condition), interleaved with sequences of neutral landscapes (neutral condition) with sequence duration 24 s. We analyzed heart rate, iEEG spectral power and neuronal spikes and compared to BOLD measurements in the same patients. **Results:** Comparing aversive versus neutral stimuli, enhanced high gamma power (HGP >60 Hz) was observed specifically in the amygdalae outside the seizure onset zone (9/14 nSOZ-amygdalae, p=0.019) while delta power (1-4 Hz) decreased in 11/11 nSOZ-amygdalae and also in 2/3 amygdalae within the SOZ. Over the group of subjects, the HGP enhancement occurred predominantly during the first 2 s of aversive sequence viewing, while the delta reduction lasted for the whole sequence (i.e. 24 s). In 5 patients with implanted microwires, single-neuron spike rates in the amygdala were enhanced following aversive stimuli. In one patient, the time course of HGP was highly correlated with heart rate (R = -.542), BOLD (R = 0.444), delta (R=0.67) and enhanced neuronal spiking (0.74). **Conclusions:** Aversive visual stimulation modulate power in the delta and high gamma frequency bands and neuronal spiking within the amygdala. The HGP specifically assessed amygdala responsiveness and might be clinically relevant for surgical planning. In summary, we

provide for the first time a comprehensive investigation of amygdala responses to aversive stimuli, ranging from single-unit spikes to local field potentials and BOLD responses.

Disclosures: **T. Fedele:** None. **B. Steiger:** None. **A. Tzovara:** None. **D. Bach:** None. **P. Hilfiker:** None. **T. Grunwald:** None. **L. Stieglitz:** None. **H. Jokeit:** None. **J. Sarnthein:** None.

Poster

714. Social and Emotional Processes

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 714.18/UU75

Topic: G.03. Emotion

Support: SAF2015-65982-R

Title: Human amygdala intracranial recordings during emotional memory encoding and recognition

Authors: M. COSTA[1], A. GIL-NAGEL[2], R. TOLEDANO[2], M. YEBRA[1], C. MÉNDEZ-BÉRTOLO[1], S. MORATTI[1,3], *B. A. STRANGE[1,4]
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Abstract: Background: Neuropsychological studies in patients with amygdala lesions have demonstrated a reduction in episodic memory for emotional stimuli. Functional neuroimaging studies have reported increased amygdala responses to emotional, relative to neutral, stimuli during memory encoding or retrieval. However, a detailed mechanistic account at the neuronal level of how emotion upregulates memory in humans is lacking. Specifically, amygdala oscillatory responses associated with successful emotional stimulus encoding, or recognition, are currently unknown. To address this, we performed direct intracranial recordings from the amygdala in epilepsy patients while they encoded and later retrieved unpleasant and neutral images.
Methods: Intracranial electrophysiological recordings were obtained from the amygdala of 11 patients (3 right, 6 left, and 2 bilateral) being evaluated for medication-resistant epilepsy. During the encoding condition, patients were presented with 120 pictures selected from the IAPS database (40 unpleasant and 80 neutral). In a second session 24h later, the same patients performed a recognition memory task: the old 120 pictures were randomly presented with 120 new pictures (40 unpleasant and 80 neutral). Patients were required to make a push-button response to indicate whether they had seen the picture before. Specifically, patients were required to make a “remember” “know”, or “new” decision. Time frequency analyses were performed to test for differential induced responses during the encoding and recognition of

unpleasant images.
Results: For the encoding session, we observed a difference of gamma activity (60-80 Hz) for unpleasant images compared to neutral from 220ms after stimulus onset. In the recognition task, we found a main effect of emotion at two frequency bands: beta2 (20-30Hz) starting from around 300ms, and high gamma oscillations (100-140 Hz) starting from around 200ms. Importantly, this gamma response was highest for old unpleasant pictures compared to the other types of stimuli.
Conclusions: Amygdala responses in the high gamma range are present not only in the perception of an emotionally salient stimuli (encoding) but also in the retrieval process of unpleasant information.

Disclosures: M. Costa: None. **A. Gil-Nagel:** None. **R. Toledano:** None. **M. Yebra:** None. **C. Méndez-Bértolo:** None. **S. Moratti:** None. **B.A. Strange:** None.

Poster

714. Social and Emotional Processes

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 714.19/UU76

Topic: H.02. Human Cognition and Behavior

Support: NIA R21 AG044862

Title: Temporal dynamics of compensatory neural response to cognitive fatigue in a 3 hour Stroop task

Authors: *I. B. SAMUEL[1], C. WANG[2], B. KLUGER[3], M. DING[2]
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Abstract: Prolonged performance of a demanding cognitive task induces cognitive fatigue. We recently demonstrated that in response to cognitive fatigue, the brain recruited neural resources that were not engaged by the task at baseline, to maintain performance. This compensatory mechanism is examined further in this study. High-density EEG (128 channels) was recorded from 15 participants between 18 and 33 years of age who performed a cued Stroop task continuously for 3 hours. Dividing the 3-hour time period into 30-minute non-overlapping time-on-task intervals we calculated the event-related potentials (ERPs) evoked by the imperative stimulus for each time-on-task interval and divided the ERPs into an early component representing mainly sensory processes (N200/P200), a mid-latency component (P300/N400) representing mainly attentional and language processes, and a late component (slow potential) representing mainly higher order cognitive control processes. While the early ERP component decreased in amplitude with time-on-task, the mid-latency ERP component exhibited a more complex pattern of response to cognitive fatigue, with the amplitude decreasing over the left

parietal region but increasing over the central frontal and right parietal regions (compensation). The rate of decline of the left-parietal ERP amplitude was significantly correlated with the rate of increase of the central-frontal and right-parietal ERP amplitude. Similarly, the late ERP component also exhibited increase in amplitude with time-on-task in the central frontal region, but decrease in amplitude over the left and right parietal regions. The rate of bilateral ERP amplitude decline was again significantly correlated with the rate of the central-frontal ERP increase. These results suggest that in distributed regions of the brain neural processing becomes impaired with the onset of cognitive fatigue and the brain employs compensatory mechanisms to cope with these impairments. In addition, owing to the exquisite temporal resolution of the ERP, we are able to uncover the temporal dynamics of the brain's compensatory response, enriching the current understanding of neural compensation derived mainly from hemodynamic studies. Given the prominent role played by neural compensation in cognitive aging this study raises the intriguing possibility that some aspects of cognitive aging may be studied using a cognitive fatigue model.

Disclosures: I.B. Samuel: None. **C. Wang:** None. **B. Kluger:** None. **M. Ding:** None.

Poster

714. Social and Emotional Processes

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 714.20/UU77

Topic: H.02. Human Cognition and Behavior

Title: The effect of motivation and valence on attentional scope: An event-related potential (ERP) study

Authors: *K. R. MICKLEY STEINMETZ[1], K. S. ARJUNE[2], P. G. BOLTON[2], A. E. BRASINGTON[2], T. J. BUNGE[2], S. V. PADULA[2], T. K. PHILLIPS[2], V. C. ZARUBIN[2]
[1]Psychology, [2]Wofford Col., Spartanburg, SC

Abstract: Previous studies have shown that valence may influence attention, with negative information narrowing attention (Easterbrook, 1959) and positive stimuli broadening it (Frederickson, 2004). However, a confounding variable may be the motivational value of these stimuli. In two studies, the influence of valence and motivation on attention was examined by looking at the N1, an early event-related potential component that has been shown to reflect focused attention. In Experiment 1, while ERP recordings were collected, participants were either primed to have global or local attention immediately before seeing pictures that were either positive and high in motivation or neutral and low in motivation. Results indicated that those primed to have focused local attention had a higher N1 amplitude when viewing positive, high motivational stimuli than neutral stimuli. In Experiment 2 participants were primed to have local attention and then viewed both negative and positive high motivational stimuli, and neutral

low motivational stimuli. Results revealed that there were no significant differences in the N1 for positive and negative stimuli. As these stimuli were matched on motivation, but not valence, this indicates that motivation is an important factor in modulating focused attention.

Disclosures: K.R. Mickley Steinmetz: None. **K.S. Arjune:** None. **P.G. Bolton:** None. **A.E. Brasington:** None. **T.J. Bunge:** None. **S.V. Padula:** None. **T.K. Phillips:** None. **V.C. Zarubin:** None.

Poster

714. Social and Emotional Processes

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 714.21/UU78

Topic: H.02. Human Cognition and Behavior

Support: Department of Science and Technology, New Delhi, India

Title: Navarasa neural correlates

Authors: *R. P. REDDY, J. RAJESWARAN
Clin. Psychology, NIMHANS, Bangalore, India

Abstract: The aim of the study was to compare the neural correlates of Navarasa (9 emotions) with Mental Health Professionals versus other professionals (n=6). All were screened on Mini-International Neuropsychiatric Interview (MINI), Standard Progressive Matrices, Interpersonal Reactivity Index (Davis,1980), Questionnaire of Cognitive and Affective Empathy (Renate at al, 2011), Emotional Quotient (Chadda) Social Stories Questionnaire (Autism Research Centre, 2002), Faux Pas Recognition Test (Simon Baron- Cohen, 1998).
fMRI Design: Navarasa Face Paradigms (9 emotions- Śṛngāram:Love, Hāsyam: Happiness, Raudram: Anger, Kāruṇyam: Compassion, Bībhatsam: Disgust, Bhayānakam: Fear, Vīram: Brave, Adbhutam: Amazement). fMRI scanning: MRI scanning was conducted in a 3 Tesla Siemens Magnetom Skyra scanner. Anatomical scan was acquired with a T1 MPRAGE sequence, with FOV w240mm, slice thickness 0.9mm, slices per slab176, voxel size 0.9*0.9*0.9mm. fMRI was acquired with an EPI sequence. The FOV was 192mm, slice thickness 4mm, slices obtained 36, voxel size 3*3*4mm, matrix 64*64, TR 4 seconds, TE .03 seconds (E prime 1.1 / Block design paradigm/ Statistical Parametric Mapping on MATLAB). Preprocessing consisted of Realignment, Normalization and Smoothing. The first level analysis was General Linear Model with Family Wise Error (FWE), $p<0.05$. One sample t test was used in the 2nd level analysis without FWE & $p<0.001$
Results: When compared to MHP and OP there was nil significant statistical difference between the groups on behavioral data. Navarasa task activated medial, superior frontal gyrus, left inferior parietal lobule, right precuneus, right angular gyrus, left occipital, right fusiform, superior

temporal gyrus, left cingulate gyrus, bilateral posterior cingulate, bilateral cingulate, and Bilateral cerebellum.

Disclosures: R.P. Reddy: None. **J. Rajeswaran:** None.

Poster

714. Social and Emotional Processes

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 714.22/UU79

Topic: H.02. Human Cognition and Behavior

Title: Electroencephalographic correlation during social decision-making in young women

Authors: *A. SIU[1], J. HEVIA[2], R. HIDALGO-AGUIRRE[1], M. PEREZ-HERNANDEZ[1], M. HERNANDEZ-GONZALEZ[1], M. GUEVARA[1]
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Abstract: In the human, decision-making consists in the process of choosing and acting at a given moment. The decision-making considers temporal factors of their environment, such as the social context, this type of decision has been called social decision-making. In this process, specific cortical areas participate, mainly the frontopolar, dorsolateral prefrontal and parietal cortices. The electroencephalographic correlation (rEEG) is an index of similarity of morphology and polarity of two electroencephalographic signals recorded simultaneously. The aim of the present study was to characterize the inter and intrahemispheric rEEG between prefrontal (frontopolar, dorsolateral) and parietal areas, during social decision-making in young women evaluated through the execution of the “Ultimatum Game” paradigm. In the "Ultimatum Game", two players are given the opportunity to split a sum of money, one is referring as the proposer and the other one as the responder. This game allows the responder decision-making to be evaluated when deciding to accept or reject a proposal in a social or non-social condition. All offers were made by a predetermined algorithm, which ensure that all participants saw the same set of offers, but in the social condition they were told that another women, who they meet at the beginning of the recording was the person who made the proposals. The participants were eighteen young women aged 20-to-30; all participants passed through both conditions. Behavioral results (total amount of money and reaction time) do not show differences when comparing performance in social and non-social decision-making, however, their brain functionality was different. During the social decision-making, participants showed a higher rEEG between frontopolar and dorsolateral, frontopolar and parietal, dorsolateral and parietal, and between both parietal cortices. This behavioral results shown that meeting the person before playing isn’t enough to generate a state of competition The higher degree of EEG coupling

among cortices could be associated with the attentional and working memory process necessary to maintain the final target while carrying out other short-term goals.

Disclosures: **A. Siu:** None. **J. Hevia:** None. **R. Hidalgo-Aguirre:** None. **M. Perez-Hernandez:** None. **M. Hernandez-Gonzalez:** None. **M. Guevara:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.01/UU80

Topic: H.03. Schizophrenia

Support: Templeton Foundation NSF BCS-1354088

NIMH 2U01MH081988-06A1

Title: Automated measures of semantic content predict conversion to schizophrenia

Authors: *N. REZAII[1], E. WALKER[2], P. WOLFF[2]
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Abstract: Introduction: Predicting conversion to schizophrenia from the prodromal stage has been hampered by a paucity of reliable biomarkers. To address this challenge, recent work has turned to statistical analyses of language. Such analyses have identified semantic coherence (cosine between adjacent sentences), word uniqueness (word Type/Token ratio), and phrase length (number of words per phrase) as predictive of conversion. One feature yet to be considered, however, is poverty of content (POC), widely considered a hallmark of the language of individuals at the prodromal and more advanced stages of schizophrenia. The current research establishes how POC can be automatically extracted from free speech and used to predict conversion to schizophrenia.
Method: The meanings of words and sentences can be extracted using word-embedding methods (e.g., Word2vec) that re-express words as vectors in a multidimensional space. The number of meaning components in a sentence can be measured using a gradient descent optimization technique that identifies the word vectors that, when properly weighted and combined, can reconstitute the meaning vector of a sentence. The number of meaning components can be used as a measure of POC. This method was applied to the transcribed answers of 29 participants of the North American Prodrome Longitudinal Study (NAPLS) to the Structured Interview for Psychosis Risk Syndromes (SIPS). Of the 29 individuals (20 high- and 9 low-risk for developing schizophrenia), seven converted to psychosis within two years of the interview.
Results and Discussion: The number of meaning components was much lower (implying poorer

content) in the converters than in the non-converters (r = .638, p = .004). Also predictive was the mean number of unique words (r = .532, p = .004). Semantic coherence (r = .133, p = .508) and sentence length (r = .240, p = .228) did not predict conversion on their own. However, logistic regression indicated that conversion could be predicted with 100% accuracy if all four linguistic parameters were included in the same model.
Conclusion: This study shows that an automated measure of POC is the *single* best biomarker for predicting conversion to schizophrenia and, when combined with several other measures, may offer a new approach to predicting conversion.

Disclosures: **N. Rezaii:** None. **E. Walker:** None. **P. Wolff:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.02/UU81

Topic: H.03. Schizophrenia

Support: NIMH grant K23-MH101637

Title: Deficient belief updating explains abnormal information seeking associated with delusions in schizophrenia

Authors: S. C. BAKER[1], A. B. KONOVA[2], N. D. DAW[3], *G. HORGA[4]
[1]New York State Psychiatric Inst., New York, NY; [3]Ctr. for Neural Sci., [2]New York Univ., New York, NY; [4]Psychiatry, Columbia Univ. Med. Ctr., New York, NY

Abstract: Delusions, a core symptom of psychosis, are false beliefs held with high conviction despite contradictory evidence. While Bayesian inference has long been proposed to underlie delusions, previous attempts to show this have not yielded compelling evidence. Here, using a modified, incentive-compatible information-sampling task in addition to well-characterized decision-making tasks, we sought a mechanistic understanding of delusional severity among a sample of 26 medicated and unmedicated patients with schizophrenia and 25 socio-demographically matched healthy controls. On each trial, participants decided whether to draw beads from one of two hidden jars - the identity of which was determined by their majority bead color, blue or green - or to guess the identity of the hidden jar, in order to minimize financial losses from a monetary endowment. Before each choice between drawing and guessing, participants gave a probabilistic estimate reflecting their confidence about the identity of the hidden jar. In stark contrast with previous work using hypothetical decision-making, patients with higher delusional severity tended to exhibit increased information seeking - both in absolute terms, compared to an ideal observer, and relative to healthy individuals. Increased information seeking (i.e., increased draws-to-decision) in patients was highly specific to delusional severity

as compared to hallucination severity, severity of negative symptoms, working-memory capacity, and other clinical and socio-demographic characteristics. Delusion-related increases in information seeking were unlikely to be driven by medication. Draw-wise probability estimates of the identity of the hidden jar further indicated that high-delusion patients had abnormal belief updating characterized by increased weight of prior evidence, a feature that correlated with increased information seeking across patients. Other decision-making parameters that may have potentially explained increased information seeking, including risk and ambiguity aversion, were unrelated to both delusional severity and information seeking among the patients. These results thus suggest that abnormal belief updating, characterized by enhanced reliance on prior information, may be a core computational feature underlying delusional belief formation or maintenance in psychosis. This computational mechanism may be a higher-level counterpart of increased reliance on prior information in hallucination-prone individuals during lower-level sensory discrimination, thus suggesting a convergent mechanism that may potentially explain psychosis more broadly.

Disclosures: S.C. Baker: None. **A.B. Konova:** None. **N.D. Daw:** None. **G. Horga:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.03/DP13/UU82 (Dynamic Poster)

Topic: H.03. Schizophrenia

Title: Response inhibition and temporal prediction errors in patients with schizophrenia

Authors: B. BOHATEREWICZ[1], M. NOWICKA[1], A. PLEWKA[2], *R. LIMONGI[3]
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Abstract: In everyday life, modifying reactions helps organisms to adjust to changeable environments. These adjustments can be achieved by implicit temporal prediction —the covert estimation of a time interval. Within the context of temporal predictions, this research compares healthy subjects to patients with schizophrenia in their ability to modify actions. A total of 15 patients with schizophrenia (the patient group, mean age = 41.73; SD = 7.47) along with 15 healthy participants (the control group, mean age = 40.93; SD = 6.68) were examined. A temporal prediction task in which subjects performed GO and STOP trials was used. On GO trials, subjects predicted collisions of two white balls with constant speed whereas on STOP trials subjects inhibited their predictions when the balls turned red. We measured prediction errors (PE, the time difference between subject's temporal predictions and actual collision times) and the stop-signal delay (SSD, the delay between the go stimulus and the stop signal) for which subjects could not succeed at inhibiting predictions on 50 % of STOP trials (SSD_{50}). Quantitative

indexes of anxiety, depression, impulsiveness, and cognitive functioning were also evaluated. Results were analyzed via mixed-effect models. On GO trials, absolute PEs were larger in the patient group than in the control group ($\beta = 56.47$; SE = 13.32; $t(28.32) = 10.48$; $p < .0001$). Both groups made larger errors when they responded before collisions than when they responded after collisions ($\beta = 30.16$; SE = 3.29; $t(4430) = 9.16$; $p < .0001$). But, the patient group responded much earlier than the control group. ($\beta = 14.00$; SE = 3.29; $t(4430) = 4.25$; $p < .0001$). On STOP trials, the SSD_{50} of the control group was larger than that of the patient group, $\beta = 148.68$; SE = 7.42; $t(1404) = 20.02$; $p < .0001$. In addition, the patient group had significantly ($p = .001$) worse cognitive performance, higher impulsiveness and higher level of anxiety and depression, than the control group. This difference could be due to premature release of prepared responses, as indexed by shorter SSD_{50} values. These results are consistent with previous studies on time perception where neuropsychiatry patients overestimated the elapsed time and were less accurate in time estimation tasks than healthy participants.

Disclosures: B. Bohaterewicz: None. **M. Nowicka:** None. **A. Plewka:** None. **R. Limongi:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.04/UU83

Topic: H.03. Schizophrenia

Support: KAKENHI 15K15428

Title: Altered auditory substrates observed in auditory verbal hallucination

Authors: *K. MATSUO
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Abstract: Auditory verbal hallucination (AVH) is a devastating symptom of schizophrenia. We hypothesized that an impairment in neural fibers, specifically, the auditory radiation (AR), would cause an alteration in the gray matter volume (GMV), and then result in aberrant activation in the auditory cortex. We investigated these neural correlates in relation with AVH scores using 3 types of MRI technologies; diffusion spectrum imaging (DSI), T1-weighted image and fMRI of language tasks. Four patients with schizophrenia who had AVH (age 25-54) and 8 controls (age 25-51) participated in this study. The severity of patients' AVH was measured using PSYRATS-J. We used 3-T MRI with a 32-ch head coil (GE Healthcare). DSI (max b-value 4000) underwent an LDDMM to transform individual data to a group template to extract fiber tracts in the same space. Generalized fractional anisotropy (GFA) was computed and extracted at each tract (100 steps each). GFA values in 25 steps of the AR adjacent to Heschl's gyrus were individually

averaged to use as the index of diffusion anisotropy. T1-weighted images were segmented into gray matter and other structures using SPM12. Voxel values of normalized, modulated and smoothed gray matter images within Heschl's gyrus were individually averaged to use as the index of GMV. For fMRI, averages of contrast estimates (task greater than fixation for both tasks) extracted from Heschl's gyrus were used as the index of activation. The GMV of Heschl's gyrus decreased according to the age advance. The GFA of patients in the AR was not greatly different from that of controls. In overall, activation levels were modest in patients as compared with controls. In view of each patient, declined GFA in the AR characterized dimensions of items in PSYRATS-J. A patient (age 45) who had a loud AVH that only came from outside his head had a low GFA in the right AR. The declined right AR might encompass a failure of locating the origin of the AVH. In contrast, another patient (age 39) who had a long-lasting, low and threatening AVH that only came from within her head had a preservation in GFA in the right AR. In her case, she showed relatively extensive activation against the GFA and GMV in left Heschl's gyrus, whereas other patients kept low levels of activation. The relative sensitivity in the left auditory cortex might indicate the persistency of her AVH.

Disclosures: K. Matsuo: None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.05/VV1

Topic: H.03. Schizophrenia

Support: D.S.T., INSPIRE Fellowship (IF140138), India

Title: Hyperctivation of left temporo-parietal regions shortens resting EEG microstates in schizophrenia

Authors: *S. SONI[1], S. P. MUTHUKRISHNAN[1], M. SOOD[2], S. KAUR[1], N. MEHTA[1], R. SHARMA[1]
[1]Physiol., [2]Psychiatry, All India Inst. of Med. Sciences, New Delhi, Delhi, India

Abstract: Background: The momentary spatial configuration of the brain electric field at the scalp reflects quasi-stable "functional microstates" caused by activity of different intracranial generators. The present study was conducted to investigate microstates' mean duration and their neural generators in schizophrenia at rest (eyes closed).
Methods: Thirty four patients with schizophrenia (diagnosed as per DSM 5, aged 18-45 years), 29 first degree relatives and 25 matched healthy controls participated in the study. EEG (eyes closed) was recorded using 128 electrodes for 5-6 minutes. EEG signal was pre-processed [band pass filter (1- 100 Hz), segmented (20 epochs of 1 second each), down sampled- 250 Hz and

artifact removal (independent component analysis)] using Net station and EEGLAB softwares. Microstate analysis was performed using Cartool software where global field power (GFP) was computed at each sample in time. K-means cluster analysis determined the most dominant classes of electric field configurations with optimal number of clusters determined by minimum value of cross-validation criterion. The spatial correlation between the microstate templates of the best solution with all the resting topographic maps were computed. Group differences of map duration were assessed using Kruskal- Wallis H test and post-hoc pairwise comparisons. sLoreta was used to compute intracerebral electrical sources of microstate maps with solution space partitioned to 6239 cubic voxels of 5 mm. The localization of global, widespread correlations between the cortical voxels activity was assessed by applying the exceedance proportion test ("cluster statistics").
Results: Kruskal-Wallis H and post hoc test showed that map 5 mean duration (MD) ($\chi^2(2)=7.617$, p= 0.022 mean rank of 35.32- patients, 48.07- relatives, 52.84- controls) was significantly lower in patients compared to controls (U= 256, p= 0.010). Statistical analyses on sLORETA images showed maximum activation in left Inferior parietal lobule (MNI coordinates: -65, -35, 25, Log-F_{max} = 0.748). Based on the exceedance proportion test suprathreshold cortical voxels (Threshold: Log-F = 0.5981, p= 0.0498) with increased activations were found localized at left superior, middle and inferior temporal gyrus.
Conclusion: Hyperactivation in left inferior parietal lobule (least studied and most important part of network affected in schizophrenia) and temporal gyri might have lead to shortening of map 5 mean duration at rest in patients with schizophrenia. This may be attributed to hallucinations and delusions in patients as normally these areas are involved in sensory integration and speech perception.

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Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.06/VV2

Topic: H.03. Schizophrenia

Support: UC San Diego FISP

UC San Diego Academic Senate

Title: Role of gamma neurofeedback in working memory of persons diagnosed with schizophrenia

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Abstract: Gamma neural oscillations are essential to working memory (WM) and other behavioral assessments. Persons diagnosed with schizophrenia spectrum disorders (SCZ) perform worse on working memory (WM) tasks compared to healthy controls (HC), and performance negatively correlates with WM load. Convergent evidence from recent studies supports the notion that gamma wave coherence (35-50Hz) over frontal brain regions is implicated in WM-task performance. SCZ patients demonstrate reduced gamma coherence compared to HC. In this context, we investigated the role of using neurofeedback (NFB, an operant conditioning EEG protocol) to improve gamma coherence in SCZ patients using a cross-over design - and, whether changes in gamma coherence were associated with changes in WM performance. Our hypothesis is improved gamma coherence in frontal cortex, will improve WM-task performance. Twelve SCZ patients, and 28 HC were recruited from University of California, San Diego. Subjects were randomized to receive gamma coherence neurofeedback training (G-NFB) or active placebo training (AP-NFB) after completing pre-treatment measures on frontal sites (F3 and F4). Pre-treatment measures were five-minute baseline EEG for each condition of eyes closed and eyes opened, EEG and behavioral n-back (WM-task), and Repeatable Battery for Neuropsychological Status (RBANS) data. After four weeks of coherence training, midpoint assessments were conducted (same as pre-treatment), and subjects were assigned to four weeks of coherence training in G-NFB or AP-NFB based on their previous training assignment. Post-treatment data measures were collected as in pre-treatment, and midpoint assessments. The study is anticipated to be completed in 06/2017, when all EEG and behavioral data will be analyzed. To date, four SCZ patients have completed the study protocol. The treatment was well tolerated with the exception of a single patient who reported motion sickness during one neurofeedback session, and subsequently discontinued participation.

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Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

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Topic: H.03. Schizophrenia

Support: FrenchNationalInstitute for Health and MedicalResearch(INSERM),

the Centre Hospitalier Régional UniversitaireofStrasbourg (API-HUS)

Title: Do anomalies in millesecond timing lead to the self-disturbances in schizophrenia? experimental, phenomenological and predictive coding approaches

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Abstract: Background
The subjective impression of continuity of time is so pervasive of our experience that we generally do not pay much attention to it. It is only when a breakdown occurs in this continuity do we notice its importance, e.g., dreaming, drug intoxication, and psychosis in schizophrenia. Patients with schizophrenia report bizarre symptoms, called "self-disturbances," in which they feel that thoughts are inserted into their minds or that their movements are controlled by foreign agents. These symptoms are called the "self-disturbances," because these experiences appear to occur independently from self. However, there is little understanding of what may give rise to them. We examine the hypothesis whether the disruption of the sense of time (time continuity) in schizophrenia patients may lead to the bizarre experience of the "self-disturbances." We proposed that these symptoms involve an inability of the subjects to automatically follow information over time at very brief, non-conscious intervals.
Methods: In a simultaneity/asynchrony implicit judgment task administered to both schizophrenia patients and healthy controls. Subjects had to decide whether the presentation of 2 squares was simultaneous or asynchronous by pressing on the left (simultaneous) or right (asynchronous).
Results: When stimulus asynchronies were too brief (<20 ms) to be detected consciously, response biases (Simon effect) were nevertheless observed in the healthy controls by pressing to the side of the second occurring square, whereas patients consistently pressed to the side of the first square. Phenomenological analysis of the data indicated that sensory events are processed at the ms level in terms of the retained information even if this information does not reach consciousness. The exhibited retentional (retained information) deficits in the patients at very brief intervals are also implicated in the self-disturbances. Surprisingly, the unconscious, automatic processing of subjective time is more accurate than conscious processing in the controls. Experimentally, the patients had difficulties to predict and follow events automatically at the ms level, which is consistent with a temporal processing impairment in the predictive coding and phenomenological accounts.
Conclusion: Self-disturbances of schizophrenia reflect disruption of lower nonconscious levels of temporal processing at very small timescales. Whereas the experimental approach highlights prediction impairments, phenomenological analysis provides testable hypotheses regarding the interaction between retention and the prediction mechanisms in the development of the self-disturbances.

Disclosures: A.L. Mishara: None. **A. Giersch:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.08/VV4

Topic: H.03. Schizophrenia

Title: Cannabis use and aberrant salience processing: Role of cannabis use variables and personality dimensions

Authors: *C. M. O'TUATHAIGH[1], A. BICKERDIKE[2], C. O'NEILL[2], P. M. MORAN[3]
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Abstract: Cannabis can induce acute psychotic symptoms in healthy individuals and exacerbate pre-existing psychotic symptoms in patients with schizophrenia. Inappropriate salience allocation is hypothesised to be central to the association between dopamine dysregulation and psychotic symptoms. The present study examined the possibility that frequency of cannabis use is associated with salience dysfunction, as indexed by self-report measures and performance in tasks measuring several salience dimensions (i.e. prediction error, emotional salience). Additionally, the study explored the relationship between salience processing and schizotypy. 910 third-level students completed a survey battery comprising the following measures: the cannabis experience questionnaire modified version (CEQmv); schizotypal personality questionnaire (SPQ); community assessment of psychic experience (CAPE); aberrant salience inventory (ASI). Kamin blocking (a measure of prediction error) and the 'white noise' salience task (emotional salience) was measured in 20 cannabis users and 20 non-users. Frequency of cannabis use and age of first exposure was associated with changes across specific sub-scales of the SPQ, as well as self-reported aberrant salience as measured by the ASI. Higher aberrant salience scores were also correlated with higher levels of positive schizotypy. Kamin blocking performance was also significantly affected by several cannabis use history variables. Consistent with earlier studies, aberrant salience is associated with increased schizotypal symptoms and history of cannabis use. This study also demonstrated that various dimensions of salience processing may be differentially affected by history of cannabis use.

Disclosures: C.M. O'Tuathaigh: None. **A. Bickerdike:** None. **C. O'Neill:** None. **P.M. Moran:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

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Program#/Poster#: 715.09/VV5

Topic: H.03. Schizophrenia

Support: Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS)

Title: Aberrant functional connectivity between thalamus and visual cortex is related to attentional impairment in schizophrenia

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Abstract: [Objective]
Schizophrenia is a severe, chronic psychiatric disorder characterized by positive symptoms, negative symptoms, and cognitive dysfunction. Attention deficit is a core feature of the cognitive dysfunction in schizophrenia and is closely linked to functional outcomes. Considerable evidence has suggested that thalamic dysfunction is related to attention deficit in schizophrenia. Resting state functional MRI (rs-fMRI) studies have revealed network dysfunction of the thalamocortical functional pathways in schizophrenia. The present study investigated the relationship between aberrant thalamocortical connectivity and attentional impairment in schizophrenia.
[Method]
Thirty-eight schizophrenic patients (20 males; mean age, 38.5 years) and 38 healthy controls (23 males; mean age, 36.2 years) underwent successive rs-fMRI and fMRI during the Flanker task. All subjects provided written informed consent to participate in the study. The ethics review committees of Nagoya University Graduate School of Medicine and Nagoya University Hospital approved this study. We identified decreased left thalamic activation (x, y, z, = -6, 10, 0) in schizophrenic patients by task fMRI in order to determine the thalamic seed. Seed-based analysis using the thalamic seed and rs-fMRI data was conducted to assess differences in thalamocortical functional connectivity between groups. Finally, we computed the correlation between degree of functional connectivity and task performance during the Flanker task in each group.
[Results]
Task performance was assessed using the Flanker effect (i.e., difference in response time between incongruent and congruent conditions), as an index of response conflict or attention. Patients showed a significantly larger Flanker effect, indicating larger distractibility by incongruent stimuli. In rs-fMRI analysis, increased functional connectivity was evident between the left thalamus seed and bilateral occipital cortices/bilateral postcentral gyri in the patient group as compared with the control group. In the patient group, significant positive correlations

($\rho = 0.44$, $p = 0.02$) between degree of connectivity from the left thalamus to bilateral occipital gyri corresponding to the visual cortex and the Flanker effect, whereas no significant correlation ($\rho = -0.15$, $p = 0.40$) was apparent in the control group.
[Conclusion]
To conclude, in schizophrenic patients, cognitive impairment as indexed by response conflict during the Flanker task may be related to increased aberrant functional connectivity between the left thalamus and visual cortex in the resting state.

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Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

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Program#/Poster#: 715.10/VV6

Topic: H.03. Schizophrenia

Support: NIMH IRP

Title: Connectome-wide association of resting-state connectivity with positive symptoms in medication-free patients with primary psychosis

Authors: ***A. BOROSHOK**[1], M. D. GREGORY[1], M. L. ELLIOTT[1], J. S. KIPPENHAN[1], J. CZARAPATA[1], D. P. EISENBERG[2], K. F. BERMAN[3]
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Abstract: Schizophrenia is a devastating illness with a range of psychopathology, including positive symptoms such as hallucinations and delusions. Though these symptoms are well-targeted by neuroleptics, their pathophysiology is not fully understood. We previously found that functional connectivity of the striatum with motor and attention networks was related to both midbrain dopaminergic tone and antipsychotic medication treatment. Dopamine dysregulation and antipsychotic medications are known to primarily impact positive symptoms in schizophrenia, though few studies relate functional connectivity to symptom severity. Here, we performed a connectome-wide association study (CWAS) to identify regions where whole-brain functional connectivity specifically related to symptom rating scores in patients tested on and off antipsychotic medications. 3T resting-state fMRI scans were collected on 17 inpatients with a history of psychosis (26.6 ± 6.8 years, 12 males) during the medicated and medication-free arms of a double-blinded, counterbalanced medication withdrawal protocol. Positive and Negative Syndrome Scale (PANSS) scores were collected and transformed to a five-factor model. After

preprocessing, CWAS analyses were performed separately for scans on and off medication to identify brain regions where connectivity related to PANSS factors. Post-hoc analyses used these significant regions as seeds in a connectivity analysis to determine the functional networks underlying the findings. Results were thresholded at $p<0.05$, FWE-corrected, with a small-volume correction using significant striatal clusters previously identified in a CWAS analyses of dopamine functioning. CWAS analyses revealed the connectivity pattern of the bilateral caudate to be related to positive symptoms while off medications. We did not find significant associations with other PANSS factors ($p's>0.05$, uncorrected) or during the antipsychotic treatment ($p's>0.2$, uncorrected). Post-hoc seed-based analyses showed that caudate connectivity with motor and dorsal attention networks drove this finding, such that greater positive symptoms were associated with greater connectivity. Here, we show that striatal connectivity with attention and motor networks is associated with positive symptoms in psychotic patients while off medications, but not during treatment. Our results extend prior findings that suggest an association of striatal connectivity with midbrain dopaminergic tone. Together, these results suggest that this pattern of striatal connectivity with attention and motor networks may be tied to the pathophysiology of psychotic symptoms.

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Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

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Topic: H.03. Schizophrenia

Support: MH111177

Title: Assessing brain activations during an "active" resting state in schizophrenia: evidence of reduced potentiation for action

Authors: *H. A. BOALBANAT[1], V. A. DIWADKAR[2], J. A. STANLEY[3], A. CHOWDURY[4], D. KHATIB[4], L. HADDAD[5], P. THOMAS[5], U. RAJAN[5], A. AMIRSADRI[5]
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Abstract: Background: The disordered patterns of connectivity and activation are characteristic of schizophrenia (Wadehra et al., 2013). Yet the functional role of rest periods in the schizophrenia brain are relatively understudied, despite evidence that the brain's functional states contribute to brain network proficiency (Diwadkar et al., 2017). Here we investigated activation

profiles in schizophrenia patients and healthy controls specifically during rest/rehearsal periods of a block-design associative learning paradigm. The paradigm required subjects to learn associations between different memoranda classes and is characterized by negatively accelerated learning (Stanley et al., 2017).
Methods: Fourteen schizophrenic patients and six healthy controls participated in fMRI (3.0T Siemens Verio). Object-location associative learning was assessed over eight cumulative epochs, over which participants were required to learn the associations between objects and the specific grid location they were presented in (9 total pairs). Each epoch alternated between encoding (27 s) and retrieval (27 s) blocks interrupted with rest blocks that were of specific interest herein (9 s). Evidence (Ravishankar et al., In Review) suggests that rest periods are characterized by coordinated and constructive brain network activity. fMRI data were processed using standard methods (SPM8). In second level random effects analyses we assessed group differences (SCZ ≠ HC) in activation during resting blocks ($p<0.5$ cluster level).
Results: The results indicate there was reduced activation across thalamic, hippocampal and frontal regions during rest periods in SCZ relative to HC. These effects are in contrast with observed evidence of hyper-activation in many of these regions during encoding and retrieval in patients (Wadehra et al., 2013).
Discussion: Sustained activity during resting epochs appears essential to underpinning task-related activity in subsequent encoding and retrieval periods of memory formation. These current emerging results suggest that a loss of engagement of brain regions at rest is a characteristic of schizophrenia, and may relate to increased physiological noise in the brain and/or the inability of the resting brain in schizophrenia to potentiate brain networks for action.

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Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

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Topic: H.03. Schizophrenia

Support: Wellcome Trust Project Grant 093270/Z/10/Z.

Niels Stensen Fellowship

Title: Delusion-like thinking is linked to glutamate concentrations and alterations in the neural mechanisms facilitating about uncertain rewards

Authors: *K. M. DIEDEREN[1], J. HAARSMA[1], T. SPENCER[2], H. ZIAUDDEEN[1], P. C. FLETCHER[1]
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Abstract: Delusional beliefs are hypothesised to arise from subtle alterations in reinforcement learning, a process dependent on dopamine and glutamate signalling. Specifically, it is thought that individuals with delusions present with altered (neural) learning patterns when outcomes are less reliable (i.e., uncertain). We sought to investigate the relationship between delusion-like thinking, learning under uncertainty and glutamate in healthy individuals.
Forty healthy volunteers predicted the value of upcoming rewards drawn from distributions with different degrees of uncertainty during fMRI scanning. On each trial, after making a prediction participants received a reward, thus yielding trial-by-trial prediction errors, learning signals that denote the mismatch between predictions and outcomes. Glutamate concentrations were measured in the prefrontal cortex and striatum in the same MRI session using MR Spectroscopy. Delusion-like thinking was assessed with the Peters Delusion Inventory. Participants were previously reported on in Diederen et al. (2016) and Diederen et al. (2017; placebo group).
As predicted, participants dampened their rate of learning as reward variability increased. The midbrain and ventral striatum adaptively coded prediction errors relative to uncertainty (Diederen et al. 2016, 2017). Individuals that scored higher on delusion-like thinking presented with a reduced tendency to attenuate learning rates as uncertainty increased. In the midbrain, the degree to which prediction errors were coded relative to uncertainty (i.e., adaptive coding) decreased as delusion-like thinking increased. Importantly, there was no significant relationship between delusion-like thinking and overall *non-adaptive* learning rates and PE coding. Delusion-like thinking furthermore correlated with glutamate concentrations.
These findings provide early support for the hypothesis that delusion-like thinking in healthy individuals is associated with changes in the degree to which learning rates and prediction errors adapt to uncertainty, rather than the strength of prediction error coding per se. Furthermore, we established a first, direct, link between delusion-like thinking, adaptive learning under uncertainty and glutamate. As such, odd beliefs may be underpinned by altered glutamate signalling and a shifted balance in the degree to which prediction errors drive learning as a function of their uncertainty.
Diederen KM, Spencer T, Vestergaard MD, Fletcher PC & Schultz W (2016). Neuron, 90(5), 1127-1138.
Diederen KM, Ziauddeen H, Vestergaard MD, Spencer T, Schultz W & Fletcher PC (2017). Journal of Neuroscience, 37(7), 1708-1720.

Disclosures: K.M. Diederen: None. **J. Haarsma:** None. **T. Spencer:** None. **H. Ziauddeen:** None. **P.C. Fletcher:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

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Topic: H.03. Schizophrenia

Support: RNAG/260

Wellcome Trust

Bernard Wolfe Health Neuroscience Fund

Title: The role of dopamine and psychosis in the precision-weighting of unsigned prediction errors in the dorsal anterior cingulate cortex

Authors: *J. HAARSMA[1], K. M. DIEDEREN[2], H. J. TAVERNE[2], J. D. GRIFFIN[2], G. K. MURRAY[2], I. M. GOODYER[3], P. C. FLETCHER[3]
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Abstract: Prediction errors form a critical signal for learning. However, they may be more or less reliable and optimal learning should take into account this reliability. Precision weighting of signed prediction errors during reward learning has been demonstrated in humans using fMRI (Diederen et al., 2016) and it is modulated by dopaminergic agents (Diederen et al., 2017). A deeper understanding of the precision weighting of prediction errors may be informative to our understanding of psychosis, which has been associated with aberrant learning. The current study sought to extend our understanding of precision weighting by focusing on unsigned prediction errors. This was done using three complementary analyses: (i) a reanalysis of existing normative data (n=28 healthy participants) (ii) a reanalysis of a pharmacological fMRI study (n=59 healthy participants receiving placebo, bromocriptine or sulpiride); (iii) a novel dataset (n=75 participants including, healthy, at-risk mental state and first episode psychosis). In each case, I focused on precision weighting of unsigned prediction errors. During fMRI data acquisition, participants estimated upcoming rewards drawn from pseudo-Gaussian distributions with varying standard deviations. An increase in SD responded to a decrease in outcome reliability. Reinforcement learning (computational) modelling of the behavioural data across all studies showed that individuals decreased their rate of learning when SD increased. Unsigned prediction errors (PEs) were coded relative to reliability (i.e., precision) as revealed by an increase in the steepness of PE regression slopes for lower SD conditions, thus signalling precision-weighting of unsigned PEs. Sulpiride perturbed precision-weighting of unsigned PEs in the dACC, and (precision-weighted) unsigned PE coding varied with the degree of delusion-like thinking (measured using the Peters Delusion inventory) irrespective of precision weighting in healthy controls. However, preliminary analyses revealed no dACC impairments in the precision-

weighting of unsigned PEs in patients with early psychosis. We conclude that coding of unsigned PEs in the dACC is precision-weighted, and may be dopaminergically mediated. Inter-individual variability in prediction error coding irrespective of precision weighting may relate to delusion-like thinking in health, but our results do not provide evidence of its disruption in psychotic illness. Possible explanations include patient heterogeneity, or that the mechanisms underpinning delusion-like thinking in health differ from delusion formation in illness.

Disclosures: J. Haarsma: None. **K.M. Diederen:** None. **H.J. Taverne:** None. **J.D. Griffin:** None. **G.K. Murray:** None. **I.M. Goodyer:** None. **P.C. Fletcher:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

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Topic: H.03. Schizophrenia

Support: Silvo O. Conte Center P50MH094268

Title: A greater tendency for mediated learning in a ketamine mouse model of schizophrenia

Authors: P. AHRENS, *M. KOH, M. GALLAGHER
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Abstract: Mediated learning is a behavioral paradigm that has been used in animal studies to potentially capture cognitive features of schizophrenia. In studies of mediated learning, representations of prior experience can enter into current associations. Using a ketamine animal model of schizophrenia, we investigated whether mice exposed to ketamine during late adolescence subsequently showed an increased tendency to use a representation of a prior gustatory experience to form associations in learning. Mice were given prior experience of an odor and a taste presented together. The odor was subsequently presented alone with gastrointestinal illness induced by a lithium chloride injection. A consumption test was then given to assess whether the taste, despite its absence during conditioning, entered into an association with the induced illness. Such learning would be *mediated* via a representation of the taste activated by the odor. Our results showed that control mice displayed no aversion to the taste following the procedures just described, but mice that had been treated developmentally with ketamine exhibited a significant taste aversion, suggesting a greater propensity for mediated learning. Chronic treatment with the antipsychotic drug, risperidone, in a different set of ketamine-exposed mice attenuated the mediated aversion learning to the taste, a finding that may be related to its known efficacy in reducing the positive symptoms of schizophrenia. These data provide a setting with potential relevance to preclinical research on schizophrenia, to study the

neural mechanisms underlying a propensity for aberrant associations and assessment of therapeutics.

Disclosures: P. Ahrens: None. **M. Koh:** None. **M. Gallagher:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

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Topic: H.03. Schizophrenia

Support: NIH Grant DK111475

Title: Associative activation and treatment of perceptual 'hedonic hallucinations' in a mouse model of neuropsychiatric illness

Authors: *A. W. JOHNSON[1], R. GIFFORD[1], C. MANNING[2], A. J. ROBISON[2], M. NIWA[3], A. SAWA[4]
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Abstract: These studies used a transgenic mouse model with a putative expression of dominant-negative disrupted in schizophrenia 1 under the under control of the prion protein promoter (DN-DISC1-Prp). Initially, we conducted a series of short-term consumption tests with water and varying concentrations of sucrose (0.1, 0.2 & 1M). An analysis of licking microstructure was adopted to examine dissociable evaluative and motivational variables that contribute to ingestive behavior. Both the mean number of licks occurring within each burst of licking (cluster size; a measure of palatability), and the frequency of initiating novel bouts of licking behavior (cluster number; a measure of motivation) were comparable in DN-DISC1-Prp and wild-type mice. Following confirmation of intact gustatory detection, we examined the capacity for a conditioned stimulus (CS) to evoke perceptual processing of an absent sucrose reinforcer. DN-DISC1-Prp and wild-type mice received training, where one CS was minimally paired with a 0.2M sucrose unconditioned stimulus (US) (16 CS-US pairings), and a second CS that was paired more extensively (112 CS-US pairings). At test, the sucrose solution was replaced with unflavored water, and the extensively trained CS evoked significantly more licks for unflavored water in DN-DISC1-Prp compared to wild-type mice. Licking microstructure revealed that the increase in licking behavior in DN-DISC1-Prp specifically reflected an increase in the perceived palatability (cluster size) of the unflavored water—i.e., a ‘hedonic hallucination’. We also examined activity-dependent neuronal changes using the marker for neuronal activity, c-fos, in brain gustatory (insular cortex) and reward areas (nucleus accumbens). In a subsequent study, systemic treatment

(0.25 mg/kg) with the typical antipsychotic, haloperidol disrupted this 'hedonic hallucination'. A final series of experiments confirmed that these effects did not reflect stimulus-response learning, impairments in extinction and/or other motivational features of reward (e.g., progressive ratio performance). Collectively, these results suggest that external stimuli (e.g., an auditory tone) can acquire control of perceptual processing of a motivational event (e.g., sucrose solution). In DN-DISC1-PrP mice this results in a highly detailed hallucination of the event (e.g., sweet taste of sucrose), even if the event is not presented, which can be treated with a typical antipsychotic. Thus, these findings provide a novel approach in animal models to examine hallucinations, which to date the assessment of which has been restricted to neuroimaging in humans.

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Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

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Topic: H.03. Schizophrenia

Support: NIH

Title: Upregulation of a brain-enriched microRNA, microRNA-124, contributes to common endophenotypes of schizophrenia and bipolar disorder

Authors: *H. NAMKUNG[1,2], H. JAARO-PELED[1], K. SHARMA[1,3], S. KANNAN[4], R. HUGANIR[3], A. SAWA[1,2,3,4]
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Abstract: For the past 5-10 years, our lab has looked for clinically detectable molecular signatures associated with schizophrenia (SZ) by using olfactory neuronal cells obtained by nasal biopsy, which are promising surrogate tissues to capture molecular signatures in neurons resulting from disease-perturbed biological networks. By conducting unbiased microarray studies together with bioinformatics analyses, we have recently underscored dysregulation of microRNA-124 (miR-124) as one of the most notable molecular signatures in SZ. We further observed that miR-124 is significantly upregulated not only in olfactory neuronal cells from patients with SZ, but also in those from patients with bipolar disorder (BP). At least in our experimental systems, miR-124 is most significantly dysregulated among representative microRNAs that have been reportedly associated with and altered in SZ and BP. To address

whether the molecular signature is driven by genetic factors, we utilized polygenic risk scores (PRSs) for SZ and BP, which aggregate genotypic scores for single nucleotide polymorphisms (SNPs) associated with psychiatric conditions. Very interestingly, the PRSs for both SZ and BP significantly predicted miR-124 upregulation, indicating that common genetic variants underlying risk of SZ and BP as their sum are likely to contribute to miR-124 upregulation. Back to biology, miR-124 is known to play crucial roles in neuronal differentiation, neurogenesis, and synaptic plasticity. To investigate miR-124 upregulation-induced endophenotypes, we next generated a mouse model by overexpressing miR-124 in the medial prefrontal cortex (mPFC) that includes brain areas homologous to human brain regions critically implicated in both SZ and BP. By the upregluation, alternation of behaviors in the constructs relevant to SZ and BP, sociability and psychostimulant sensitivity, was observed. Furthermore, we examined the effect of miR-124 upregulation on glutamatergic synaptic transmission properties. We found that upregulation of miR-124 alters AMPA-R subunit composition and therefore synaptic transmission properties. We finally showed the causality of the alteration in the AMPA-Rs on the behavioral deficits. Together, the present study indicates that excessive miR-124, which is driven by common genetic risks of SZ and BP, critically disturbs AMPA-R mediated synaptic transmission that underlies pathological changes in key behavioral constructs relevant to both SZ and BP.

Disclosures: H. Namkung: None. **H. Jaaro-Peled:** None. **K. Sharma:** None. **S. Kannan:** None. **R. Huganir:** None. **A. Sawa:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.17/VV13

Topic: H.03. Schizophrenia

Title: The Dysbindin-1A isoform selectively modulates basal ganglia-related phenotypes through astrocytic-dependent functioning

Authors: *R. MASTROGIACOMO[1], D. MAURO[1], V. FERRETTI[1], A. FORGIARINI[2], F. MANAGÒ[1], R. MAROTTA[1], D. ROTHMOND[3], J. L. WADDINGTON[4], C. S. WEICKERT[3], G. ORSO[5], F. PAPALEO[1]
[1]NBT, Iit, Genova, Italy; [2]Inst. of Pediatric Research, IRP, Padova, Italy; [3]NeuRa Fndn., Sydney, Australia; [4]Royal Col. of Surgeons in Ireland, Dublin 2, Ireland; [5]IRCCS E. Medea Scientific Inst., Conegliano, Italy

Abstract: Dysbindin-1 is a protein implicated in vesicular trafficking, synaptic plasticity and clinical response to antipsychotic drugs, and its expression is altered in schizophrenia. Dysbindin-1 exists in different isoforms (1A, 1B, 1C) with region-, subsynaptic- and

developmental-specific expression. However, their specific functional roles remain unknown. Using a novel floxed mouse line, we demonstrated that life-long selective disruption of the dysbindin-1A isoform (dys1A) was sufficient to produce unexpected selective molecular and behavioral phenotypes consistent with basal ganglia, but not cortical-dependent alterations. In particular, dys1A disruption resulted in increased D2 receptors on cells surface in the striatum, sensorimotor gating deficits, hyperactive phenotypes (similarly to dys1 mice with full knockout of all isoforms), as well as impairments in serial reversal learning and motivation. In contrast to dys1 full knockout, D2 expression in PFC, social and attentional set-shifting abilities were not affected by dys1A disruption. Notably, postmortem human brain analyses revealed that dys1A, but not dys1C, was reduced in the caudate of patients with schizophrenia compared to matched healthy subjects. Using a Drosophila model of dysbindin-1 disruption, we found a primary effect on morphological features and survival of astrocytes. Moreover, in mice we found that dys1A is the only isoform expressed in glial cells, and dys1A knockout mice show altered golgi complex selectively in astrocytes. Strikingly, selective knockout of dys1A in astrocytes and during adulthood (Dys1AGlast) was sufficient to recapitulate the dys1A phenotype. These findings strongly suggest a genetic-driven mechanism selectively regulating basal ganglia astrocytic functioning, opening new avenues in the biology of glial dopaminergic mechanisms potentially implicated in psychiatric disorders and related pharmacological treatments.

Disclosures: R. Mastrogiacomo: None. **D. Mauro:** None. **V. Ferretti:** None. **A. Forgiarini:** None. **F. Managò:** None. **R. Marotta:** None. **D. Rothmond:** None. **J.L. Waddington:** None. **C.S. Weickert:** None. **G. Orso:** None. **F. Papaleo:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.18/VV14

Topic: H.03. Schizophrenia

Support: McNulty Civitan Scholar Award

Title: ERRα as a putative mediator of PGC-1α-dependent gene expression: Relevance for the pathophysiology of Schizophrenia

Authors: *L. J. MCMEEKIN[1], L. M. JENKINS[1], B. M. WATKINS[2], A. S. BOHANNON[1], A. PATEL[1], A. KRALLI[3], J. J. HABLITZ[1], R. M. COWELL[1]
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Abstract: The transcriptional coactivator peroxisome proliferator activated receptor gamma coactivator-1 alpha (PGC-1α) is a known regulator of transcripts involved in neuronal function,

including neurotransmission, morphology and metabolism. Importantly, polymorphisms in PGC-1α have been linked to schizophrenia and bipolar disorder. Studies from our lab indicate a reduction in the PGC-1α-dependent transcripts synaptotagmin 2, complexin 1, neurofilament heavy chain and parvalbumin in the cortex, without changes in PGC-1α expression. The mechanisms underlying these changes in gene expression are not clear. We show here that a potential mediator of PGC-1α effects in the brain is orphan nuclear receptor estrogen-related receptor α (ERRα). Promoters of PGC-1α-dependent transcripts contain binding sites for members of the ERR family, ERRα inverse agonists block PGC-1α-driven gene expression, and ERRα knockout mice exhibit reductions in PGC-1α dependent genes in cortex and hippocampus. Interestingly, while ERRα null mice do not show overt motor abnormalities seen in PGC-1α null mice, these mice show impairments in prepulse inhibition, similar to mouse models of schizophrenia. These studies highlight the cell and circuit-specific roles for ERRα in the brain and suggest that modulation of this pathway could be explored for the rescue of discrete endophenotypes in psychiatric disease.

Disclosures: L.J. McMeekin: None. **L.M. Jenkins:** None. **B.M. Watkins:** None. **A.S. Bohannon:** None. **A. Patel:** None. **A. Kralli:** None. **J.J. Hablitz:** None. **R.M. Cowell:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.19/VV15

Topic: H.03. Schizophrenia

Support: Santos Dumont Institute

AASDAP

FINEP

INCEMAQ (Programa INCTs do CNPq/MCT)

FAPERN

CAPES

CNPq

Title: Arduino-based prepulse inhibition behavioral box: A low cost method for schizophrenia symptoms assessment

Authors: *L. ANDREOLI[1], E. MORYA[2]
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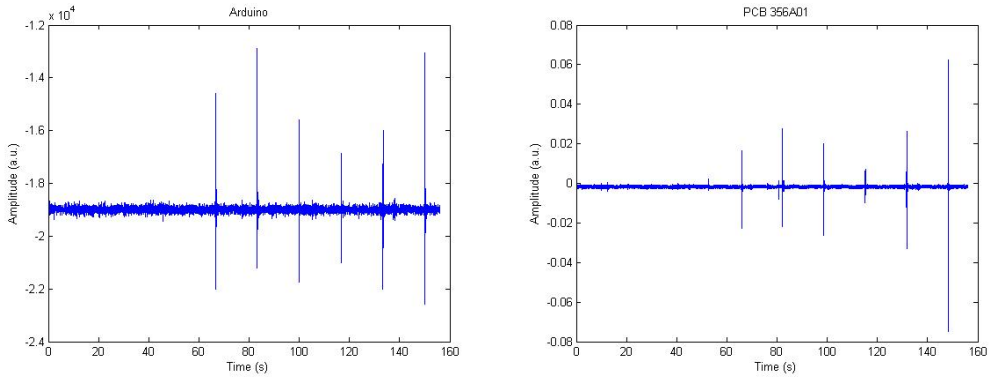
Abstract: Patients suffering from psychosis lack the ability to inhibit their responses to incoming sensory information and select from diverse sensory input which information is relevant. Prepulse inhibition (PPI) is a widely accepted paradigm to assess sensory filtering deficits both in patients with schizophrenia and animal models of the disease. PPI consists of inhibition of a startle reflex in response to a sudden and intense stimulus (usually a loud acoustic noise of ~120 dB) by presenting a weaker pulse (usually of ~65 dB, which does not elicit startle responses) 30 to 500 ms before the loud pulse. In schizophrenia, this phenomena is disrupted and startle response magnitude is not diminished when a weak stimulus precedes a stronger pulse. Arduino based behavioral box tests are widely increasing in research laboratories due to its cost and the possibility to customize experiments. We developed a do it yourself (DIY) behavioral box to assess prepulse inhibition and other startle response measures with Arduino interface. To detect animal startle responses, we used an Arduino Uno microcontroller and an accelerometer (MPU6050, InvenSense), fixed in a rodent behavioral box. To test the behavioral box accuracy , we compared the recorded acceleration with that from a more sophisticated system, namely a Triaxial Ceramic Shear Accelerometer (PCB 356A01, 5 mV/g, PCB Piezotronics) and a Nidaq amplifier (NI cDAQ 9138 CompactDAQ, National Instruments). Our benchmark test shows that the Arduino-accelerometer device is as effective in detecting movement in the behavioral box as more expensive sensors and it is sensitive to rodents startle (Fig 1). In addition, this box can be built and customized with components commonly found in a neuroscience laboratory, thus substituting more expensive devices.



Disclosures: **L. Andreoli:** None. **E. Morya:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.20/VV16

Topic: H.03. Schizophrenia

Support: Biomedical Research Foundation Louisiana

Title: Neurogranin regulates sensorimotor gating through cortico-striatal circuitry

Authors: *B. GO, J. M. SULLIVAN, III, A. N. REKER, H. W. NAM
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Abstract: Prepulse inhibition (PPI) is the normal suppression of startle reflex when a strong startling pulse is preceded by a prepulse and the sensory prepulse inhibits (gates) the motor startle response. PPI provides an operational measure of sensorimotor gating and PPI deficits are shown in schizophrenia (SZ) patients. Genetic variants or decreased neurogranin (Ng) gene are observed in SZ patients and may regulate hypo-frontality in SZ. Therefore, in the present study, we examined whether Ng in the cortico-striatal circuitry plays essential roles in sensorimotor gating measured by PPI. In Ng knock out ($Ng^{-/-}$) mice, PPI response was significantly reduced compared to WT mice, which suggests that Ng is required for normal sensorimotor gating function. To examine brain-specific role of Ng and its PPI associations, we used viral-mediated gene expressions, optogenetics, and designer receptors exclusively activated by designer drugs (DREADD) stimulation. Using brain-specific Adeno-Associated Virus (AAV)-mediated Ng expression, we identified that Ng overexpression in the medial prefrontal cortex (mPFC) but not in nucleus accumbens (NAc) was effective to increase PPI response. This indicates that Ng in the mPFC has a functional role in regulating PPI response. To further examine cell type-specific PPI regulation in mPFC-NAc circuit, excitatory neuron-specific (CaMKII) optogenetics and inhibitory neuron-specific (parvalbumin; Pv) DREADD were utilized. The excitatory neuron - specific optogenetic stimulation in the PFC-NAc circuit showed higher PPI response, whereas PFC- and NAc-specific stimulation, respectively, did not show any changes in PPI response. In addition, inhibitory neuron-specific DREADD stimulation in either mPFC or NAc showed no changes in PPI response compared to baseline. In this study, we identified that Ng expression in the mPFC is positively correlated with PPI response. Moreover, the Ng in the mPFC and the NAc has shown brain region- and neuron subtype-specific effect in PPI response, indicating that molecular signaling cascades differently affect the schizophrenic behaviors depending on the brain region and/or neuronal subtypes.

Disclosures: B. Go: None. **J.M. Sullivan:** None. **A.N. Reker:** None. **H.W. Nam:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 715.21/VV17

Topic: H.03. Schizophrenia

Support: NIMH Grant MH090067

SALSI postdoctoral fellowhip (S.M.Perez)

Title: Schizophrenia-like behavioral deficits can be reproduced by regional knockdown of parvalbumin or somatostatin interneurons in the prefrontal cortex or ventral hippocampus

Authors: *A. M. BOLEY, S. M. PEREZ, D. J. LODGE
Pharmacol., UTHSCSA, San Antonio, TX

Abstract: Schizophrenia is a psychiatric disorder characterized by three types of symptoms – positive, negative, and cognitive. GABAergic deficits are consistently detected post-mortem in the hippocampus of schizophrenia patients and we posit they contribute to positive symptoms of the disease. Interneuron deficits are also seen in cortical areas such as the prefrontal cortex, which are likely to underlie negative and cognitive symptoms. Specifically, alterations in both parvalbumin-containing (PV) and somatostatin (SST) containing interneurons are consistently observed in patients; however, whether these deficits contribute to, or are a consequence of, the pathology of schizophrenia has not been established. Here, we examine region specific reductions of PV or SST in the medial prefrontal cortex (mPFC) or ventral hippocampus (vHipp) utilizing a lentiviral-mediated shRNA to knockdown (kd) expression of these GABAergic subtypes. We postulate that this specific knockdown of PV or SST will result in aberrant neuronal activity and discrete behavioral changes associated with schizophrenia. Rats with PV or SST kd in the mPFC, exhibited a decrease in social interaction, a correlate of the social withdrawal observed in schizophrenia patients. To examine cognitive flexibility, rats performed the attentional set-shifting assay. In rats with PV kd in the mPFC, deficits in reversal learning were observed. Single cell extra-cellular recordings of putative pyramidal neurons of the mPFC suggest that average firing rate and pattern are not affected by PV or SST kd. In addition, dopamine neuron activity in the ventral tegmental area (VTA) was analyzed. Predictably, manipulations to the mPFC did not affect VTA dopamine neurons, as population activity has been shown to be driven by the vHipp. Indeed, we have previously demonstrated that a decrease PV GABAergic interneurons in the vHipp is sufficient to recapitulate the dopamine system dysfunction commonly observed in rodent models of the disease and patients, as well as model positive symptoms. Here, we report the effects of hippocampal PV and SST kd on negative and cognitive behaviors. Taken together, this data suggests specific interneuron populations in discrete brain regions differentially contribute to distinct behavioral deficits associated with schizophrenia.

Disclosures: **A.M. Boley:** None. **S.M. Perez:** None. **D.J. Lodge:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

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Program#/Poster#: 715.22/VV18

Topic: H.03. Schizophrenia

Support: MRC (grant codes MC_U142684173)

NARSAD Young Investigator Award to Michael Parsons

Title: Comparison of allelic mutations in the L-type calcium channel subunit CACNA1c, a risk factor in neuropsychiatric diseases

Authors: *P. LAU[1], E. HOBBS[1], V. TUCCI[2], G. LASSI[2], M. PARSONS[1], G. T. BANKS[1], P. M. NOLAN[1]
[1]MRC Harwell Inst., Harwell Campus, United Kingdom; [2]Neurobehavioural Genet. Group, Neurosci. and Brain Technologies, Genova, Italy

Abstract: Neuropsychiatric disorders such as schizophrenia and bipolar disorder have a large genetic component with symptoms including: anxiety, alternation in drive or emotional states, cognitive deficits and sleep/circadian disturbances. Despite this diversity in symptoms, separate Genome-Wide Association Studies have linked the L-type calcium channel subunit, *CACNA1C*, to both schizophrenia and biopolar disorder. In addition, a specific *CACNA1C* mutation has also been associated with autism and major depressive disorder, suggesting that *CACNA1C* may be a shared genetic risk factor across the psychiatric disorder spectrum. In order to validate these associations, we sought to develop mouse models that can be used to study the physiological function of *CACNA1C*. However, since knockouts of this gene in the mouse are homozygous lethal, we have screened an *N*-Ethyl-*N*-Nitrosourea mutagenized mouse archive for additional allelic variants that express more subtle and varied behavioural phenotypes.
In this study, we identified two mutations in *Cacna1c* (missense and truncation in the same domain) showing endophenotypes associated with schizophrenia and bipolar disorder. Molecular and anatomical analyses were used to investigate *Cacna1c* expression mutant primary neurons and tissues. The functional effects of the mutations were analysed using *in vitro* calcium imaging assays. The mutant mouse lines also underwent a battery of phenotyping tests with an emphasis on endophenotypes of neuropsychiatric symptoms including anxiety and cognitive deficits. We found that animals with either missense or truncation mutations show opposing anxiety-related behaviours. For example, in the open field test, missense mutants showed decreased anxiety and increased exploratory behaviour, otherwise characterised as 'mania' - an endophenotype of bipolar disorder. The same behaviours are not shared by the animals with truncated *Cacna1c*. These animals are more anxious and explore less, which is consistent with symptoms observed in schizophrenia and depressive disorder. Further tests of anxiety such as Elevated Plus maze partially validated these findings. Additionally, the truncation mutant mice show sleep fragmentation, which is notable as *CACNA1C* has also been implicated in narcolepsy, a feature often observed in patients with psychiatric diseases. Together our results suggest that these two mutant lines might be useful animal models for psychiatric disorders that have a diverse endophenotypes.

Disclosures: P. Lau: None. **E. Hobbs:** None. **V. Tucci:** None. **G. Lassi:** None. **M. Parsons:** None. **G.T. Banks:** None. **P.M. Nolan:** None.

Poster

715. Clinical and Animal Studies of the Symptoms of Schizophrenia

Location: Halls A-C

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Program#/Poster#: 715.23/VV19

Topic: H.03. Schizophrenia

Support: CIHR

NSERC

Title: Reduced synapsin II expression in the medial prefrontal cortex of rats manifests behavioural and brain metabolic changes: Implications in the pathophysiology of schizophrenia

Authors: A. M. BERNARDO[1], S. THOMSON[2], *L. P. NILES[3], R. K. MISHRA[1]
[1]Psychiatry and Behavioural Neurosci., [2]Life Sci., [3]HSC-4N77, Psychiat & Behav Neurosci, McMaster Univ., Hamilton, ON, Canada

Abstract: Schizophrenia (SZ) is a psychiatric disorder with few antipsychotic drugs (APDs) alleviating the associated spectrum of symptoms. Negative and cognitive symptoms, which can manifest as social withdrawal and memory impairment respectively, evade current APDs. Treating SZ relies on targeting APDs to the underlying pathophysiology thus, elucidation is crucial for SZ APD design. Synapsin II (SynII) is a neuronal phosphoprotein responsible for synaptic vesicle trafficking of multiple neurotransmitters involved in SZ. SynII has been implicated in SZ through genome wide association studies and reduced SynII mRNA levels in SZ post-mortem studies. To consolidate SynII's role in SZ, our study explored SZ-like behavioural phenotypes and brain metabolic changes after SynII knockdown (KD) in rats. A scrambled control or SynII lentiviral-mediated shRNA was infused *in vivo*. Rats were then tested for negative symptoms using a social interaction paradigm, and cognitive symptoms, specifically working memory, using the 8-arm radial maze (8-ARM). Brain metabolic activity was also investigated. After cognitive stimulation using the 8-ARM, computerized tomography and positron emission test images were fused for accurate region-specific glucose metabolism profiles. Behavioural results showed SynII KD animals spent significantly less time interacting in comparison to control rats, in the social interaction paradigm, consistent with social withdrawal-like behaviour. The 8-ARM revealed a significant increase in the total number of errors made by SynII KD animals, indicative of working memory deficits. Further, functional brain imaging revealed a global neural hyperactivation in SynII KD animals compared to controls. These behavioural changes and altered glucose metabolism are consistent with those found in SZ. Our findings corroborate reduced SynII in the pathophysiology of SZ and reinforce SynII as a potential therapeutic target to alleviate negative and cognitive symptoms of SZ.

Disclosures: **A.M. Bernardo:** None. **S. Thomson:** None. **L.P. Niles:** None. **R.K. Mishra:** None.

Poster

716. Biochemical and Signaling Techniques

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 716.01/VV20

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Subcellular localization of non-prenylatable Rho GTPases and its implication in signal cascades

Authors: ***N. G. RAUT**[1], J. M. REDDY[2], D. L. HYNDS[3]
[1]Biol., Texas Women's Univ., Denton, TX; [2]Biol., [3]Texas Woman's Univ., Denton, TX

Abstract: The Rho guanine triphosphatase (GTPase) are highly characterized GTPase proteins that act as molecular switches operating between an active GTP-bound state and an inactive GDP-bound state. Precise regulation of activity in the Rho family of guanosine triphosphatases (GTPases) is necessary for proper development and functioning of the nervous system, and alterations in Rho GTPase signaling are implicated in a variety of neurodegenerative and neurotraumatic disorders. RhoA promotes assembly of focal adhesion complexes and the organization of actin cytoskeleton. Similarly, Rac1 stimulates the peripheral actin accumulations, membrane ruffling and formation of lamellipodia and filopodia. 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, localization of active RhoA and Rac1 and cell signaling pathways. Western blot analysis suggested less cofilin associated with the cytosol than membranes after transfection with the wildtype RhoA construct. ERK and JNK phosphorylation was increased in cytosol. With emerging evidence of differential activation of Rho GTPases based on their subcellular localization, elucidating the signaling cascades of the active GTPases may identify the distinct functions of these GTPases and can be used as novel targets to facilitate axon regeneration in traumatic or degenerative neurological conditions.
This research was supported by the TWU Department of Biology, Research Enhancement, Closing the GAPs. 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. **D.L. Hynds:** None.

Poster

716. Biochemical and Signaling Techniques

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 716.02/VV21

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: UTMB Mitchell Center for Neurodegenerative Disease

Title: Multiprotein complexes in plasticity

Authors: *L. A. DENNER[1], E. ISHIMWE[2], I. CORTEZ[2], E. HOSSAIN[1], K. T. DINELEY[2]
[1]Intrnl. Med., [2]Neurol., Univ. Texas Med. Br., Galveston, TX

Abstract: Multiprotein complexes allow rapid, fine-tuned integration and processing of diverse stimuli driving cellular responses that underlie physiological processes such as new gene transcription. In the periphery, ERK MAPK (extracellular-signal regulated kinase) forms a central node in multiprotein complexes that execute cellular processes as ubiquitous, yet diverse, as cell proliferation, differentiation, transformation, and death. The composition of these transcription complexes is key to conferring specificity between extracellular signals and the nucleus through temporally dynamic assembly of scaffolds to affect nuclear localization and recruitment of coregulators for new gene transcription. A fundamental problem is that we lack an understanding of ERK multiprotein transcription complexes in the CNS at the necessary resolution to achieve biologically relevant interventions (e.g., cognitive enhancement). Dysfunctional ERK multiprotein complexes contribute to neurological diseases such as Huntington's, Parkinson's, and Alzheimer's disease and it is clearly established many forms of memory consolidation require ERK-dependent gene transcription. We recently discovered that, in animal models of aging and disease, PPARγ (peroxisome proliferator activated receptor-γ) establishes a nuclear multiprotein complex with ERK that is necessary for hippocampal memory consolidation.
In this study, we established an *in vitro* model system to recapitulate ERK-PPARγ multiprotein complexes for transcriptional competency. We found that: 1) PPARγ transcriptional activity is ERK-dependent, 2) nuclear co-localization of ERK-PPARγ complexes requires ERK activity (pERK), 3) PPARγ phosphorylation occurs during this process, and 4) CREB binding protein (CBP) is a component of ERK-PPARγ complexes. Thus, we have validated a model system to recapitulate the MEK/ERK/CREB/CBP signaling pathway and it's modulation by the nuclear receptor, PPARγ. This model system forms the launching point for subsequent studies interrogating ERK-PPARγ multiprotein complexes in new gene transcription, plasticity and memory formation.

Disclosures: L.A. Denner: None. **E. Ishimwe:** None. **I. Cortez:** None. **E. Hossain:** None. **K.T. Dineley:** None.

Poster

716. Biochemical and Signaling Techniques

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 716.03/VV22

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: DFG-RTG 1960

GSfBS UoC

Title: Revealing the peptide inventory of neurons belonging to an insect locomotor system

Authors: *S. LIESSEM, S. NEUPERT, A. BÜSCHGES, R. PREDEL
Zoological Dept., Univ. of Cologne, Köln, Germany

Abstract: In insects, considerable information on the operation and organization of neural networks in the thoracic ganglia is available that underlie the generation of the default locomotor patterns for jumping, flying and walking. One thoroughly studied insect species, with respect to terrestrial locomotor behavior, is the Indian stick insect *Carausius morosus*. In the recent years, many studies revealed detailed information on neuronal mechanisms, which are involved in the control of walking and contributing to behavioral flexibility such as changing walking direction, speed of walking or turning. However, sparsely knowledge exists on the set of neuroactive substances like neuropeptides and protein hormones that are involved in the generation and modulation of these motor activities.
To fill this gap, we investigated the neuropeptidome of C. morosus as complete as possible by means of different mass spectrometric approaches. Furthermore, we use transcriptome data to verify our neuropeptidomic analyses. In total, 159 novel and likely bioactive neuropeptides and protein hormones were found derived from 46 precursors.
In the next step, this information will be used to get insight into the neuropeptidergic modulation of motoneurons and the premotor microcircuitry that drives locomotion. Therefore, we used single cell profiling by MALDI-TOF mass spectrometry to restrict the number of putative neuropeptides, which could be involved in locomotion processes. Preliminary mass spectrometric results revealed myoinhibitory peptides (MIP) as potential candidates. To confirm these findings, immunocytochemistry is being added to our experimental pipeline. To investigate the physiological function of MIP in the locomotor network, electrophysiological recordings will be conducted in future experiments during drug application.

Disclosures: S. Liessem: None. **S. Neupert:** None. **A. Büschges:** None. **R. Predel:** None.

Poster

716. Biochemical and Signaling Techniques

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Program#/Poster#: 716.04/VV23

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: National Honor Scientist Program

KHT R&D project grant-HI14C1891

Title: Development of LC3-GABARAP sensors containing a LIR and a hydrophobic domain to monitor autophagy and its application in neurological disorders

Authors: *J.-A. LEE[1], Y.-K. LEE[1], Y.-W. JUN[2], H. CHOI[1], Y. HUH[4], B.-K. KAANG[5], D.-J. JANG[3]
[1]Hannam Univ., Dajeon, Korea, Republic of; [2]Kyungpook Natl. Univ., Sang-Ju City, Korea, Republic of; [3]Kyungpook Natl. Univ., Sangju-si/gyeongsangbuk-Do, Korea, Republic of; [4]Korea Basic Sci. Inst., osong, Korea, Republic of; [5]Departments of Biol. Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Macroautophagy allows for bulk degradation of cytosolic components in lysosomes. Overexpression of GFP,RFP-LC3/GABARAP is commonly used to monitor autophagosomes, a hallmark of autophagy, despite artifacts related to their overexpression. Here, we developed new sensors (HyD-LIR-GFP) that detect endogenous LC3-GABARAP proteins at the autophagosome using an LC3-interacting region (LIR) and a short hydrophobic domain (HyD). Among HyD-LIR-GFP sensors harboring LIR motifs of 34 known LC3-binding proteins, HyD-LIR(TP)-GFP using the LIR motif from TP53INP2 allowed detection of all LC3/GABARAPs-positive autophagosomes. However, HyD-LIR(TP)-GFP preferentially localized to GABARAP/GABARAPL1-positive autophagosomes in a LIR-dependent manner. In contrast, HyD-LIR(Fy)-GFP using the LIR motif from FYCO1 specifically detected LC3A/B-positive autophagosomes. HyD-LIR(TP)-GFP and HyD-LIR(Fy)-GFP efficiently localized to autophagosomes in the presence of endogenous LC3/GABARAP levels and without affecting autophagic flux. We are currently modifying the numbers of LIR motifs and its combination with other motifs for its application as a selective autophagy marker on various neurological disorders.

Disclosures: J. Lee: None. **Y. Lee:** None. **Y. Jun:** None. **H. Choi:** None. **Y. Huh:** None. **B. Kaang:** None. **D. Jang:** None.

Poster

716. Biochemical and Signaling Techniques

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 716.05/VV24

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Temporal characteristics and behavioral consequences of chemogenetic oxytocin neuron activation

Authors: *T. GRUND[1], R. MENON[2], S. PROBST[2], V. GRINEVICH[3], I. D. NEUMANN[2]
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Abstract: Oxytocin (OT) is well described for its anxiolytic, pro-social, and fear-attenuating effects (Neumann, 2008; Lukas et al., 2011; Zoicas et al., 2014). Herein, we analyzed the spatio-temporal dynamics of chemogenetic OT neuron activation within the rat hypothalamic paraventricular nucleus (PVN) using designer receptors exclusively activated by designer drugs (DREADDs), and its behavioral relevance. Although DREADDs allow selective activation (or inhibition) of specific neuronal populations (Armbruster et al., 2007) in order to dissect their contribution to complex behaviors and brain circuitries, the spatio-temporal dynamics of DREADD actions with respect to OT neurons remain unknown. After viral vector-based expression of an excitatory DREADD (hM3Dq) specifically in OT neurons, we monitored the dynamics of OT release within PVN, lateral septum, and peripheral blood following chemogenetic stimulation initiated by clozapine *N*-oxide (3 mg/kg, ip). Central OT release in the PVN and septum was monitored by microdialysis technique, while peripheral OT release was analyzed in plasma samples collected via jugular vein catheter. Our results demonstrate that OT release peaks 45-90 min following chemogenetic activation, which correlated with behavioral changes, such as an induction of anxiolysis, increase of self-grooming, and attenuation of ethanol intoxication, which peaked 1h following DREADD-induced activation of OT neurons. Furthermore, in social fear conditioned mice, the activation of OT neurons (1h prior to fear extinction) profoundly facilitated social fear extinction. Altogether, these results narrow down the time window, when chemogenetic stimulation of neuropeptidergic neurons can be efficiently applied for studying behavioral changes. Furthermore, our findings demonstrate that chemogenetic manipulation of OT neurons is a powerful tool for dissection of novel functional OT brain circuits and hence various OT-dependent behaviors in normal and psychopathological conditions.

Disclosures: T. Grund: None. **R. Menon:** None. **S. Probst:** None. **V. Grinevich:** None. **I.D. Neumann:** None.

Poster

716. Biochemical and Signaling Techniques

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 716.06/VV25

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: DA11697

T32DA07268

NIHR37 EB003320

Title: Protein kinase c inhibitors attenuate amphetamine-stimulated dopamine overflow

Authors: *A. G. ZESTOS[1], M. E. GNEGY[2], R. T. KENNEDY[3]
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Abstract: Over 13 million people are affected by amphetamine abuse, and there is currently no therapeutic for amphetamine addiction. Amphetamine serves as a substrate for the dopamine transporter (DAT) and reverses the transporter to cause dopamine overflow in addition to inhibiting the vesicular monoamine transporter (VMAT) to promote dopamine exocytosis. Activation of the beta subunit of protein kinase C (PKCβ) increases extracellular dopamine in the presence of amphetamine by enhancing the reverse transport of dopamine and internalizing the D2 autoreceptor. We used in vivo microdialysis with liquid chromatography-tandem mass spectrometry (LC-MS/MS) in live, behaving rats to assess the effect of the PKCβ inhibitors enzastaurin and ruboxistaurin on amphetamine-stimulated increases in catecholamines and their metabolites. A 30 min perfusion of the nucleus accumbens core with 1 μM enzastaurin or 1 μM ruboxistaurin reduced amphetamine-stimulated overflow of dopamine and its metabolite 3-methoxytyramine by approximately 50%. The inhibitors also significantly reduced extracellular levels of norepinephrine and its metabolite normetanephrine after amphetamine. The stimulation of locomotor behavior by amphetamine, measured simultaneously with the analytes, was reduced by the PKCβ inhibitors. Novel PKC inhibitor 6c also attenuated amphetamine-stimulated dopamine overflow when delivered locally and systemically (simultaneously with amphetamine and 18 hours prior). Ruboxistaurin also attenuated cocaine stimulated extracellular dopamine, a process that would not be dependent upon DAT reversal. In order to see if this process was D2 autoreceptor mediated, we examined the effect of ruboxistaurin on cocaine activation when D2 receptors were blocked with raclopride before ruboxistaurin administration. The inhibitory effect of ruboxistaurin was reduced in the presence of cocaine and raclopride, suggesting that ruboxistaurin action involved D2 autoreceptors. Using a stable isotope label (SIL) retrodialysis procedure, we determined that ruboxistaurin had no effect on basal levels of dopamine,

norepinephrine, glutamate, or GABA. Our results support the utility of using PKCβ inhibitors to reduce the effects of amphetamine.This research is funded by DA11697, T32DA007268, and NIHR37 EB003320.

Disclosures: **A.G. Zestos:** None. **M.E. Gnegy:** None. **R.T. Kennedy:** None.

Poster

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Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Polish NCN Grant to MK (2015/17/B/NZ4/02016)

Title: Clozapine N-oxide, the DREADD agonist, does not affect learning-dependent cortical plasticity

Authors: *G. DOBRZANSKI, R. ZAKRZEWSKA, M. LIGUZ-LECZNAR, M. KOSSUT
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Abstract: The main idea behind the mode of action of the Designer Receptors Exclusively Activated by Designer Drug (DREADD) technique is that selective designer receptors agonist, clozapine N-oxide (CNO) is pharmacologically inert: it does not act like an agonist for native receptors and not affect other cell signaling pathways, thus does not induce unspecific behavioral outcomes. Recently, however, a study has reported that administration of CNO alone altered schizophrenia-like behavioral performance in one of the rat strain, emphasizing the need of establishing CNO control groups in chemogenetic experiments. Although in mice CNO was not reported to affect behavior, we checked it in experimental model of associative fear learning, in which stimulation of vibrissae paired with tail shock results in plastic modification of the barrel cortex activation. Expansion of the functional cortical representation of the row of whiskers activated during conditioning was revealed with 2-deoxyglucose autoradiography (Siucinska and Kossut, 1996). This experiment stands as a starting point for our further chemogenetic research aiming to assess a role of different interneuron subtypes in learning-dependent cortical plasticity. A group of wild type C57BL/6J mice underwent behavioral training consisting of 3 sessions of conditioning in three consecutive days. 30 minutes before each session mice were injected intraperitoneally with CNO (1 mg/kg). 24 hours after the third session 2-deoxyglucose brain mapping was performed. Autoradiograms of brain sections containing the barrel field were analyzed and functional representation of the conditioned row of whiskers and contralateral row on the other side of the snout were mapped. Analysis of 2-deoxyglucose labeling showed enlarged representation of the trained row in the fourth layer of barrel cortex in conditioned hemisphere in comparison to the control one. Cortical activation was also observed in other

structures like secondary somatosensory cortex and auditory cortex, which replicates the pattern of activation observed in previous experiments. The results suggest that CNO administered alone, at dose that was shown to produce unspecific behavioral results in of the rat strain, does not influence the cortical plasticity evoked by associative fear conditioning within the barrel cortex and can be employed in further chemogenetic experiments within this experimental model of learning in mice.

Disclosures: G. Dobrzanski: None. **R. Zakrzewska:** None. **M. Liguz-Lecznar:** None. **M. Kossut:** None.

Poster

716. Biochemical and Signaling Techniques

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Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Grants-in-Aid for Scientific Research (16K20875)

Akiyama Life Science Foundation research grant 2014

Title: Whole-brain activity mapping using the immediate-early promoter-driven reporter system in the cricket

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[1]RIES, Hokkaido Univ., Sapporo-Shi, Japan; [2]JT Biohistory Res. Hall, Takatsuki-Shi, Japan

Abstract: Genes expressed in response to increased neuronal activity are widely used as neuronal activity markers in recent behavioral neuroscience. In the present study, we established transgenic reporter system for whole-brain activity mapping in the two-spotted cricket *Gryllus bimaculatus*, a hemimetabolous insect used in neuroethology and behavioral ecology. First, we identified cricket homologues of four candidate neuronal immediate-early genes (IEGs): (i) *fos-related antigen* (*fra*), (ii) *jun-related antigen (jra),* (iii) *early growth response* (*egr*; an insect homologue of vertebrate *Egr-1/Zif268/NGFI-A/Zenk*), (iv) *hormone receptor 38* (*hr38*; an insect homologue of *NGFI-B/nur77/NR4A1*), and examined their expression characteristics in the brain. In the cricket brain, *Gryllus fra-B, egr-B* and *hr38* genes were inducible expressed in response to neuronal hyperexcitability caused by picrotoxin (PTX) injection. The inducible expression of these genes was resistant to inhibitors of protein synthesis, indicating these genes are expressed as neuronal IEGs. in addition, these neuronal IEGs showed differential expression time-courses after PTX treatment, as well as differential sensitivity to pharmacological activation of various intracellular signaling pathways. Next, we isolated the gene regulatory region of *Gryllus egr-B.* A 2.2 kbp genomic fragment upstream to the translation initiation site of *Gryllus egr-B* was

contained potential binding sites for stimulus-regulated transcription factors (e.g. CREB, AP-1, SRF), as well as core promoter elements and two *cis*-regulatory modules conserved across insect/crustacean *egr-B* homologues. Using the gene regulatory region of *Gryllus egr-B,* we established an immediate-early promoter-driven transgenic reporter system in the cricket. The reporter gene expression cassette contained the gene regulatory region of *Gryllus egr-B* and a nuclear-targeted destabilized EYFP (*EYFPnls::PEST*), and was integrated into the cricket genome by using the *piggyBac* transposon-mediated gremlins transformation. In the brain of transgenic crickets, the reporter gene was inducibly expressed after PTX injection, and the expression levels of the reporter gene and *Gryllus egr-B* were strongly correlated. Besides, inducible expression of reporter protein was detected in almost all neurons after PTX treatment. Our novel transgenic reporter system allows us to map the neuronal activity at cellular resolution in the cricket brain.

Disclosures: T. Watanabe: None. **A. Ugajin:** None. **H. Aonuma:** None.

Poster

716. Biochemical and Signaling Techniques

Location: Halls A-C

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Program#/Poster#: 716.09/VV28

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Magnetic sorting of glutamatergic synaptosomes using a recombinant extracellular tag

Authors: *E. A. BROWN[1], L. J. SEVERS[3,4], P. WOO[3,5], S. E. P. SMITH[2]
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Abstract: Research on synaptic biochemistry is important for understanding synaptopathies such as autism, epilepsy, and Alzheimer's, but current methods used to isolate synapses for biochemical analysis have several functional limitations. Sucrose gradients are traditionally used to enrich resealed synapses (synaptosomes) from brain homogenates, but roughly half of the fraction of interest is made up of non-synaptic cell debris. Additionally, the population of synapses isolated in these synaptosome preparations is heterogeneous, which limits the study of individual synapse types and can contribute to poor signal-to-noise. We have developed a method to quickly purify glutamatergic synapses from traditional synaptosome preparations using magnetically activated cell sorting (MACS) technology. We designed a protein construct that consists of PSD95 (with a PDZ domain deletion) to act as an anchor at glutamatergic synapses, GFP, and truncated extracellular CD4 to allow a high-affinity binding by MACS reagents. After confirming synaptic localization of the construct *in vitro,* we expressed it *in vivo* using a lentiviral vector. We isolated P2 synaptosomes from mouse brain homogenate and used

magnetic microbeads and columns to separate CD4-tagged synapses from the preparation with magnetic columns. We compared the P2 synaptosome preparation and magnetically sorted population at each step using both flow cytometry and western blotting, and found several-fold enrichment of native PSD95 and other glutamatergic synaptic proteins after magnetic sorting. Ongoing work aims to develop an additional protein tag expressed at only recently active glutamatergic synapses, and to analyze the biochemical properties that differentiate them from inactive synapses. This method can be used to isolate other synapse types by changing the construct's anchor, and has the potential to boost signal to noise ratio in downstream applications and allow detection of subtle changes in synaptic properties that can provide insight into their function and disruption in disease.

Disclosures: E.A. Brown: None. **L.J. Severs:** None. **P. Woo:** None. **S.E.P. Smith:** None.

Poster

716. Biochemical and Signaling Techniques

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Program#/Poster#: 716.10/VV29

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Lawrence Livermore National Laboratory LDRD 16-ERD-035

Title: The effect of the neural environment on lifetime of enzymatic biosensors for neurotransmitter detection

Authors: *A. M. YORITA, S. CHEN, A. TOOKER, A. M. BELLE
Lawrence Livermore Natl. Lab., Livermore, CA

Abstract: We are studying the effects of the neural environment on the lifetime of enzymes immobilized on microelectrode array biosensors. Current electrochemical methods of neurotransmitter detection in near-real time in the brain involve the oxidation of neurotransmitters at the surface of a microelectrode. While some neurotransmitters are electrochemically active, others require an enzyme layer to catalyze the synthesis of an electrochemically active molecule (typically hydrogen peroxide) when the neurotransmitter of interest is present. Integration of these chemical sensors into a multifunctional microelectrode array is a vital next step towards understanding the relationship between chemical and electrophysiological signaling in the brain. However, the lifetime of these enzyme layers is significantly lower than the lifetime of sensors for electrophysiological recordings, especially upon implantation. Once implanted into the brain, enzymatic biosensors typically last on the order of days to weeks, whereas electrophysiological sensors have a lifetime of months to years. Thus, it is necessary to understand which aspects of the neural environment are most important in affecting lifetime such that we can work on improving the lifetime of the biosensor array.

We aim to understand the parameters affecting the lifetime of the immobilized enzyme layer by examining the environment to which it is exposed upon implantation. Specifically, we are studying the enzyme glutamate oxidase, which is used to detect the presence of glutamate. A polymer-based, flexible microelectrode array was fabricated, onto which glutamate oxidase was immobilized. The biosensors were then exposed to a variety of parameters, including aqueous environments at elevated temperatures with chemicals typically found in the brain. We then measured the change in sensitivity to glutamate over the course of weeks to track the lifetime of the immobilized glutamate oxidase layers. This understanding of the factors decreasing sensitivity and thus sensor lifetime is the first step in extending the lifetime of enzymatic sensors for chronic use in behavioral studies. With these results, the next step is to examine methods that will better stabilize the enzyme, thus leading to an improved implantable lifetime for biosensors.

Disclosures: **A.M. Yorita:** None. **S. Chen:** None. **A. Tooker:** None. **A.M. Belle:** None.

Poster

716. Biochemical and Signaling Techniques

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Program#/Poster#: 716.11/VV30

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: W.M. Keck Center for Behavioral Biology

Title: Novel lactate oxidase-modified carbon-fiber microbiosensor for monitoring rapid lactate fluctuations in the rat striatum using fast-scan cyclic voltammetry

Authors: *S. SMITH[1], S. GOSRANI[1], M. DAUSCH, 27695[1], C. A. LEE[2], G. MCCARTY[4], L. A. SOMBERS[3]
[2]Chem., [3]Dept Chem., [1]North Carolina State Univ., Raleigh, NC; [4]Pine Res. Instrumentation, Durham, NC

Abstract: Traditionally, it has been thought that glucose is the principal energy source of the brain. Recently, this widely accepted concept has been challenged by several studies demonstrating lactate as an important molecule with an essential role in energy metabolism and memory formation. As such, real-time molecular detection of lactate dynamics is imperative to understanding brain energy availability, and its involvement in neuropathological disorders such as Alzheimer's disease. However, to date, existing methods for detecting brain lactate concentrations are limited in terms of temporal and spatial resolution. We have addressed this need by developing and characterizing a novel lactate oxidase-modified carbon-fiber microbiosensor and coupling it with fast-scan cyclic voltammetry. This approach enables detection of rapid lactate fluctuations with unprecedented spatiotemporal resolution as well as excellent stability, selectivity, and sensitivity at discrete recording sites in the rat striatum. It can

be coupled with our previously developed glucose-oxidase microbiosensor to enable simultaneous detection of both essential non-electroactive molecules. Combined, these new tools enable quantitative investigation of limitations to brain metabolism in disease states.

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Poster

716. Biochemical and Signaling Techniques

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Program#/Poster#: 716.12/VV31

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Autoradiography methodologies in CNS research

Authors: J. RYTKÖNEN, T. PARKKARI, *O. M. KONTKANEN, A. J. NURMI, T. HUHTALA
Charles River Discovery, Kuopio, Finland

Abstract: Autoradiography is a powerful technique that can be applied to study cerebral blood flow, receptor density and activation of G protein-coupled receptors (GPCRs) by novel pharmacological compounds in the brain. These methodologies are easily applicable to various disease models, and combining them with behavioral readouts allows a versatile evaluation of pathophysiology of the CNS disorders and mechanisms of action of novel therapies. GPCRs are involved in a wide variety of physiological processes, including regulation of behavior and mood. They activate intercellular signal transduction pathways and cellular responses. Cannabinoid, serotonin, dopamine, GABAB, and metabotropic glutamate receptors are among neurologically interesting GPCR targets. Ligand binding to GPCRs induces an interaction of the receptor with G protein that stimulates the release of GDP simultaneously with the exchange of GTP. ^{35}S-GTPγS autoradiography has been applied to study receptor activation after ligand binding to GPCRs of Gi and Gs types. In this study, we analyzed changes in the receptor density in rodent neurological disease models. To assess receptor density alterations, tritiated ligands to dopamine receptors 1 and 2, serotonin transporters and cannabinoid receptor 1 (CB1) were used and Bmax values of corresponding ligands were determined in relevant brain regions. Changes in Bmax values correlate with alterations in the number of available receptors sites and which may correlate with the phase or severity of the disease. We also determined the dose-response relationship of GPCR activation by the CB1 agonist HU-210 by detecting consumption of GTPγ^{35}S in the somatomotor cortex, cingulate cortex, striatum, globus pallidus and substantia nigra in mice. The potency (half maximal effective concentration, EC50) as well as efficacy (Emax) of interaction of HU-210 with CB1 was calculated from the obtained dose-response curves. The current examples demonstrate how a combination of assays can be utilized to

advance our understanding of the disease state and measure effects of pharmacological treatments. Also, applied digital scintillation autoradiography enables quantitative and real-time imaging of tritiated samples within hours, compared to minimum of several weeks of exposure time required to phosphoscreens or films. This accelerates method development and analysis substantially. As a summary, the combination of receptor and functional autoradiography offers a powerful tool to comprehensively measure changes in disease models or responses to novel molecules.

Disclosures: J. Rytkönen: None. **T. Parkkari:** None. **O.M. Kontkanen:** None. **A.J. Nurmi:** None. **T. Huhtala:** None.

Poster

716. Biochemical and Signaling Techniques

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Program#/Poster#: 716.13/VV32

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NCSU OUR Summer Research Grant

Title: Quantitative comparison of enzyme immobilization strategies for real-time glucose detection employing fast scan cyclic voltammetry

Authors: *S. GOSRANI, S. K. SMITH, L. Z. LUGO-MORALES, C. TANG, G. S. MCCARTY, S. KHAN, L. A. SOMBERS
Chem., North Carolina State Univ., Raleigh, NC

Abstract: Electrochemical detection of non-electroactive species, such as glucose, requires biosensors which are stable, selective, and have physiologically relevant sensitivities to targeted analytes. Glucose oxidase, an enzyme, enables the electrochemical detection of glucose through the production of hydrogen peroxide. This hydrogen peroxide is electroactive and serves as the glucose reporter molecule. We have demonstrated sub-second electrochemical detection of glucose fluctuations by combining glucose oxidase modified carbon fiber microelectrodes with fast-scan cyclic- voltammetry (FSCV). FSCV has the ability to distinguish different electroactive species while maintaining effective temporal resolution and sensitivity. Carbon-fiber microelectrodes are used in conjunction with FSCV to detect electroactive molecules. The sensing surface of the microelectrode can be enzymatically modified to create biosensors. The work presented herein quantitatively compares three approaches for enzyme immobilization - physical adsorption, hydrogel entrapment, and electrospinning - on a carbon-fiber microelectrode. The data suggest that each of these methods can be used to create functional microbiosensors; however, of these, hydrogel entrapment is the most effective approach to glucose oxidase immobilization on the carbon electrode surface. These implications are useful

because they define an effective strategy for microbiosensor fabrication that is broadly applicable to other oxidase enzymes, allowing the detection of non-electroactive molecules such as choline and glutamate. Overall, tools such as these will enable researchers to study multiple facets of neuroscience and tackle problems surrounding the detection of non-electroactive molecules.

Disclosures: S. Gosrani: None. **S.K. Smith:** None. **L.Z. Lugo-Morales:** None. **C. Tang:** None. **G.S. McCarty:** None. **S. Khan:** None. **L.A. Sombers:** None.

Poster

717. Optogenetics Methods

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Program#/Poster#: 717.01/VV33

Topic: I.04. Physiological Methods

Title: Simultaneous optogenetic manipulations and cellular resolution calcium imaging during active behavior using a head-mountable miniaturized microscope

Authors: *A. M. STAMATAKIS, M. J. SCHACHTER, S. GULATI, S. MALANOWSKI, M. TRULSON, S. OTTE
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Abstract: The ability to precisely monitor and manipulate neural circuits is essential to understand the brain. Advancements over the last decade in optical techniques such as calcium imaging and optogenetics have empowered researchers to gain insight into brain function by systematically manipulating or monitoring defined neural circuits. Combining these cutting-edge techniques enables a more direct mechanism for ascribing neural dynamics to behavior. Here, we developed a miniaturized integrated microscope that allows for cellular-resolution calcium imaging and optogenetic manipulation in freely behaving mice. We developed and tested this technology to minimize biological and optical crosstalk. We have demonstrated the utility of this technology by probing the causal relationship between circuit function, behavior, and network dynamics in neural circuits involved in motivated behaviors. This integrated strategy will allow for routine investigation of the causality of circuit manipulation on cellular-resolution network dynamics and behavior.

Disclosures: A.M. Stamatakis: A. Employment/Salary (full or part-time):; Inscopix. **M.J. Schachter:** A. Employment/Salary (full or part-time):; Inscopix. **S. Gulati:** A. Employment/Salary (full or part-time):; Inscopix. **S. Malanowski:** A. Employment/Salary (full or part-time):; Inscopix. **M. Trulson:** A. Employment/Salary (full or part-time):; Inscopix. **S. Otte:** A. Employment/Salary (full or part-time):; Inscopix.

Poster

717. Optogenetics Methods

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Topic: I.04. Physiological Methods

Support: NIH R01 MH107620

New York Stem Cell Foundation

NSF GRFP

Title: Influence Mapping: All-optical, causal measurement of effective microcircuit connectivity in mouse cortex

Authors: *S. CHETTIH, C. D. HARVEY
Harvard Med. Sch., Boston, MA

Abstract: To achieve a mechanistic understanding of the function of neural circuits, it is essential to relate activity patterns observed in a neural population to the underlying structure of the network. Existing methods towards these ends, like connectomics and paired patch-clamp recordings, can probe mono-synaptic connectivity in functionally characterized neurons. However they are low-yield, terminal, and technically challenging experiments. We have developed a complementary measurement of a novel quantity we call influence: the effect of spiking activity in one cell on the spiking activity of each other cell in a network. The measurement requires causally triggering spikes in an identified neuron and measuring the resulting change in activity in other neurons. We note that influence is related but complementary to mono-synaptic connectivity patterns. Specifically, influence may change as a function of brain state, as well as reveal emergent, multi-synaptic effects which are difficult to predict from mono-synaptic connectivity matrices.
To measure influence, we use an all-optical approach based on simultaneous two-photon calcium imaging and two-photon photostimulation of neurons co-expressing GCaMP6 and C1V1 or ChrimsonR. We modified channelrhodopsins to enrich cell body localization and reduce densities in axons and dendrites, resulting in reliable activation of nearly all expressing cells with single-neuron resolution. In initial experiments in mouse V1 L2/3, we measured influence between neurons and characterized tuning properties in the same neural population. We then analyzed how influence between neurons was related to multiple dimensions of functional similarity between stimulated and responding neuron, as well as the spatial extent of these effects. Influence was spatially and functionally structured consistent with predictions from known mono-synaptic connectivity: influence was weak beyond ~250 micrometers and inhibitory on average despite stimulating only excitatory cells. Also, influence between

individual pairs correlated with similarities in functional tuning. These measurements provide a direct estimate of how local processing in mouse V1 L2/3 shapes neural representations. More broadly, influence mapping experiments have high sampling (~10,000 neuronal pairs per experiment), are rapid (3-5 hours in duration), and can be performed repeatedly across weeks and in various behavioral states. We anticipate that the influence measurement developed here affords new opportunities for insight into neural circuit function in learning and behavior.

Disclosures: S. Chettih: None. **C.D. Harvey:** None.

Poster

717. Optogenetics Methods

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Topic: I.04. Physiological Methods

Title: Causal mapping of brainwide dynamics by activity-targeted circuit perturbation

Authors: *N. VLADIMIROV[1], Y. MU[2], J. D. WITTENBACH[2], J. FREEMAN[2], S. PREIBISCH[1], M. AHRENS[2]
[1]Max-Delbrueck Ctr., Berlin, Germany; [2]HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Controlled perturbations of neural activity are crucial for discovering causal interactions in neural circuits. Neuronal targets for activation and silencing tend to be selected by anatomical location or genetic identity. Much power would be added to experiments if it were possible to perturb large brainwide populations of neurons chosen by how their activity patterns relate to specific aspects of behavior.
We introduce a system for deleting large populations of individual neurons specified by their activity patterns during behavior across the entire larval zebrafish brain. Responses of neurons during behavior are first mapped throughout the brain using light-sheet imaging and fast computational analysis. Selected by response properties and location, groups of individual neurons are then deleted by two-photon laser ablation. Post-perturbation, whole-brain activity and behavior are again recorded and differences analyzed, all in the same fish. We apply this method to brain-wide neuronal responses during visually-evoked swimming behavior. We map the effects of the deletion of specifically-tuned neurons on neural activity and behavior, and find multiple loci that perturb whole-brain dynamics and behavioral responses.
This concurrent whole-brain activity and causality mapping in the same animal promises new insights into the contributions of neuronal populations to brain-wide dynamics and behavior.

Disclosures: N. Vladimirov: None. **Y. Mu:** None. **J.D. Wittenbach:** None. **J. Freeman:** None. **S. Preibisch:** None. **M. Ahrens:** None.

Poster

717. Optogenetics Methods

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Topic: I.04. Physiological Methods

Support: Hong Kong Research Grants Council (HKGRC)

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Title: Low frequency hippocampal-cortical activity drives brain-wide resting-state functional connectivity: An optogenetic functional MRI study

Authors: *R. W. CHAN[1,2], A. T. L. LEONG[1,2], E. C. WONG[1,2], L. C. HO[1,2], P. P. GAO[1,2], C. M. DONG[1,2], Y. S. CHAN[3], L. W. LIM[3], E. X. WU[1,2]
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Abstract: The hippocampus, including the dorsal dentate gyrus (dDG), and cortex engage in bidirectional communication. We propose that low frequency activity in hippocampal-cortical pathways underlies brain-wide resting-state connectivity to mediate distinct cognitive functions and integrate sensory information. Since the DG primarily receives cortical terminal projections and acts as a bridge for cortico-hippocampal-cortical network communication, we examined how spatiotemporally specific activity initiated in the dDG influences cortical activity and subsequent brain-wide resting-state functional connectivity by combining optogenetic, cell-specific stimulation of CaMKIIα-expressing excitatory neurons (i.e., dDG granule cells) and large-scale functional MRI (fMRI) detection. Low (0.5-2 Hz), but not high (40 Hz), frequency stimulation of dDG excitatory neurons evoked robust cortical and subcortical fMRI responses. Subsequent local field potential (LFP) recordings revealed that only low frequency stimulation evoked strong LFP responses in bilateral V1, corroborating the fMRI results, though all tested stimulation frequencies evoked LFP responses in dDG. LFP latency measurements indicate that the first evoked responses occurred in the ipsilateral dDG and propagated to the ipsilateral V1 polysynaptically (9.5±1.3ms, $p < 0.001$), before reaching contralateral V1 via monosynaptic interhemispheric callosal connections (4.0±1.5ms, $p < 0.01$). In addition, interhemispheric resting-state fMRI (rsfMRI) connectivity was enhanced in dorsal hippocampus (dHP), primary visual (V1), primary auditory (A1) and primary somatosensory (S1) cortices during and after low, but not high, frequency stimulation. We further observed an increase in infra-slow (<0.1 Hz) rsfMRI BOLD activity in dHP, V1, A1 and S1 during and after low frequency stimulation. Subsequent LFP recordings revealed an increase in slow oscillations in dorsal hippocampus and

visual cortex, interhemispheric visual cortical connectivity, and hippocampal-cortical connectivity. Visually-evoked fMRI responses in visual regions were also increased during and after low frequency dDG stimulation. In addition, after low frequency dDG stimulation, long-term but not short-term memory was improved in novel-object recognition test compared to sham. Our results indicate that low frequency activity propagates in hippocampal-cortical pathway, drives interhemispheric cortical rsfMRI connectivity, mediates visual processing and coordinates long-term memory.

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Poster

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NeuroSeeker n°600925

Title: High-density µLED probes on flexible and stiff substrates

Authors: *E. KLEIN, S. AYUB, C. GOSSLER, O. PAUL, P. RUTHER
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Abstract: This paper reports on optical implants with integrated micro light-emitting diodes (µLED) on flexible or rigid substrates for optogenetic applications. The process flow is based on a 6-µm-thick GaN layer grown on a sapphire substrate which is transferred to a carrier wafer [1,2] and subsequently released from the sapphire substrate using a laser-lift-off (LLO) process [3]. This sophisticated wafer-level fabrication process is designed to realize high-density µLEDs arrays for flexible surface probes and rigid penetrating optical probes. The radiant flux of these µLEDs is measured to be 3.5 mW/mm^2 at a current density of 0.5 A/mm^2 for both types of implants, which is sufficient for optogenetic experiments.
In the case of the rigid penetrating probes, the µLEDs are transferred to silicon (Si) wafers which are further processed using deep reactive ion etching and grinding of the wafer [4] to release single probes similar to our Michigan-style recording probes. The direct integration of µLEDs onto the Si probes enables a considerable shrinkage of the overall probe dimensions at an increased LED density compared to probes realized using chip-level LED integration [5]. In

addition to the probe dimensions and µLED density, the wafer-level manufacturing improves the probe precision and the overall process yield. As an example, probes with a shaft length of 8 mm comprising 10 µLEDs at a pitch of 150 µm have been realized. The probes are suitable for acute animal experiments requiring a depth controlled optical stimulation.
For the flexible probes, µLEDs are transferred to a polymer thin film substrate comprising thin-film interconnects and bond pads. The support wafer is equipped with an innovative release mechanism based on sacrificial layers, which guarantees the optimal adhesion of the polymeric substrate during probe processing and enables a stress-free probe release once the probes are finished. The probe technology allows to realize 30-µm-thin flexible probe shanks with integrated GaN µLEDs in a wafer-level fabrication process. The probes achieve bending radii of at least 500 µm enabling the probe insertion into a mouse cochlea [2]. We processed probes of different sizes with shank lengths from 5 to 15 mm as well as 2D arrays both comprising up to 144 µLEDs individually addressable in a matrix configuration. The minimal µLED size realized so far is 50×50 μm^2 at a pitch of 100 µm.
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Poster

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Title: Single-scan, whole-brain functional network mapping using optogenetic fMRI with CBV

Authors: *A. WEITZ[1], M. CHOY[2], B. DUFFY[2], J. LIU[2], J. LEE[1]
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Abstract: The combination of optogenetic stimulation with simultaneous fMRI readouts (ofMRI) is an effective method for mapping the brain-wide causal influence of specific genetically- and spatially-defined neuronal populations. However, a limitation shared by previous ofMRI studies has been the large number of scans needed before signal changes are detected. To take full advantage of the ofMRI toolbox, whole-brain functional network mapping should ideally be achievable in a single scan. Here, we investigated whether measurement of cerebral blood volume (CBV) by use of a superparamagnetic iron oxide nanoparticle (SPION)-based contrast agent could enable robust single-scan detections during optogenetic brain stimulation.

To address this question, we used channelrhodopsin to stimulate excitatory neurons of the thalamic submedial nucleus in adult Sprague-Dawley rats (N=13). Prior to imaging, the SPION contrast agent Feraheme was administered through the tail vein to visualize the CBV response. Optical stimuli were presented as a block-design paradigm, with six cycles of 20s stimulation trains presented every minute. In a subset of subjects (N=5), a second series of experiments was conducted to compare single-scan activations between blood-oxygen-level-dependent (BOLD) and CBV measurements. Three consecutive scans of BOLD were collected, followed by three more scans measuring the CBV response after SPION injection.

Standard general linear model analysis techniques could detect significant brain-wide fMRI activations after a single CBV scan. The strongest signals were observed at the site of stimulation and ventrolateral orbital cortex, a major projection site of the stimulated nucleus. Time series from these regions exhibited high SNR, suggesting that robust signal modulations can be measured from a single CBV ofMRI scan. Other regions modulated by stimulation included striatum and motor/somatosensory cortex. When we directly compared BOLD and CBV in the same animal and session with identical anesthetic conditions, we found that BOLD measurement led to minimal activations while CBV again gave robust brain-wide activations. After quantifying total activation volume, we found that single-scan CBV measurements resulted in significantly more activations than a three-scan average of BOLD.

These data confirm that CBV ofMRI is a viable method for single-scan functional brain network mapping. In particular, the improvement in sensitivity afforded by CBV means that brain-wide network dynamics can be visualized and analyzed resulting from only a single - in our case, six minute - scan.

Disclosures: **A. Weitz:** None. **M. Choy:** None. **B. Duffy:** None. **J. Liu:** None. **J. Lee:** None.

Poster

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NSF CAREER Award (1056008)

Title: Carbon fiber electrodes for single-unit recording combined with artifact-free MRI

Authors: *M. E. CHUAPOCO[1,2], B. A. DUFFY[2], H. J. LEE[2], M. CHOY[2], J. H. LEE[2,3,4]
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Abstract: Combining electrophysiology and optogenetic functional magnetic resonance imaging (ofMRI) allows for cellular and network-level investigation of the brain. However, implanted metal microelectrodes used for extracellular depth recordings produce susceptibility artifacts that distort MR images. Recent work in our lab and others has shown that carbon-fiber bundles are a suitable electrode design for simultaneous local field potential (LFP) recordings and ofMRI, but there remains a need to demonstrate that carbon fiber probes can be used for single-unit recording without significantly distorting MR images. To address this need, we adopted an electrode design that uses a single carbon-fiber (~10µm in diameter) functionalized with the conductive polymer PEDOT:pTS and assess its applicability for unit recording and artifact-free MRI.

To quantify the electrical performance of PEDOT:pTS electrodes compared to commonly used metal microelectrodes, we measured the impedance of electrodes across a broad range of frequencies relevant to electrophysiology recordings (1Hz-5kHz). While uncoated carbon-fiber electrodes have higher impedance values compared to silver, platinum-iridium, and tungsten microelectrodes, all fabricated PEDOT:pTS electrode groups have lower impedance values compared to the three metal microelectrodes tested. When viewed using scanning electron

microscopy, the tips of the PEDOT:pTS electrodes show clear morphological changes due to the PEDOT:pTS functionalization. Additionally, when implanted into an agarose phantom, PEDOT:pTS electrodes distort a smaller volume of voxels compared to metal electrodes. These results demonstrate that an electrode design made from a single carbon-fiber may be ideal when trying to combine electrophysiology and ofMRI, as it has superior electrical properties and distorts a smaller volume of voxels compared to commonly used metal microelectrodes. To highlight the in vivo recording capabilities of PEDOT:pTS electrodes, we recorded spontaneous LFP and spiking activity in CA1 of rat hippocampus. PEDOT:pTS electrodes were capable of recording multi-unit activity and after offline spike sorting, distinct single units can be clearly identified. As such, this work lays the foundation for an electrode design that can be used to conduct electrophysiology and artifact-free ofMRI simultaneously. Using a probe that can record LFP and unit activity without distorting MR images during ofMRI will enable us to capture more information in regions of interest and enable us to build a more complete functional model of the brain.

Disclosures: M.E. Chuapoco: None. **B.A. Duffy:** None. **H.J. Lee:** None. **M. Choy:** None. **J.H. Lee:** None.

Poster

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Title: Motor- versus sensory- neuron selective optogenetic stimulation. Cell autonomously enhanced axon regeneration

Authors: *P. J. WARD, S. CLANTON, A. ENGLISH
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Abstract: Brief neuronal activation in injured peripheral nerves is both necessary and sufficient to enhance axon regeneration, and this effect is specific to the activated motoneurons. It is unknown whether sensory neurons respond in a similar manner to neuronal activation following peripheral axotomy. Furthermore, it is unknown to what extent enhancement of axon regeneration with increased neuronal activity relies on a reflexive interaction within the spinal circuitry. We used mouse genetics and optical tools to evaluate the specificity and selectivity of system-selective neuronal activation to enhance axon regeneration in a mixed nerve. MODEL:

We evaluated sensory and motor axon regeneration in two different mouse models expressing the light-sensitive cation channel, channelrhodopsin (ChR2). We selectively activated sensory or motor axons using light stimulation immediately prior to transection and repair of the sciatic nerve. Regardless of genotype, the number of ChR2-positive neurons was greater following system-selective optical treatment, with no effect on the ChR2-negative neurons (whether motor or sensory neurons). CONCLUSIONS: Until now, it has been impossible to limit neuronal activation to sensory or motor axons alone in a mixed nerve. Medical advances will soon make this a possibility in human patients and may have desirable or undesirable effects on functional recovery depending on the nerve to be treated.We conclude that acute system-selective neuronal activation is sufficient to enhance motor and sensory axon regeneration. This regeneration-enhancing effect cell autonomous.

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Poster

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W.M. Keck Foundation

Title: Genetically encoded light sources for non-invasive optogenetics

Authors: *T. M. BROWN[1], G. G. LAMBERT[2], A. PAL[1], M. PRAKASH[1], N. C. SHANER[2], U. HOCHGESCHWENDER[1]
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Abstract: Optogenetics is the use of light to manipulate light sensing molecules, opsins. Activation of these light-gated ion channels and pumps, when expressed by neurons, results in depolarization or hyperpolarization of cell membranes. This allows activation and silencing of neuronal circuits in behaving experimental animals via light fibers implanted into the animal's brain. We proposed a strategy for non-invasive optogenetics by switching out the light source from an invasive physical to a non-invasive biological one, i.e., a light producing protein, or luciferase. The luciferase emits light, activating the optogenetic actuator upon application of its

small-molecule substrate, coelenterazine (CTZ). We engineered fusion proteins of a light-emitting luciferase to an optogenetic light-responsive element, resulting in a luminescent opsin, or luminopsin. Activation of fused opsins will be more efficient as the light emission of the luciferase increases. One way to increase light output of luciferases is to couple them to fluorescent proteins to take advantage of BRET (bioluminescent resonance energy transfer). This class of probe is far brighter than the parental luciferase enzyme because the quantum efficiency of emission is governed not by the luciferase enzyme, but rather by the fluorescence quantum yield of the BRET acceptor. We performed mutant library screenings in E. coli towards directed evolution of luciferases to improve their enzymatic activity and towards linker length, composition, and domain geometry of BRET probes for optimization of their efficiency. The brightest new BRET probes were codon-optimized and fused to optogenetic actuators. Fusion proteins were expressed in primary cultured neurons and assessed for their effects on activating and silencing neurons in multi electrode arrays (MEAs). New luminopsin constructs had robust expression, increased light emission compared to previously used luciferase variants, and showed efficient activation of opsins by increasing and decreasing spiking of cultured neurons.

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Poster

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Title: Bioluminescence driven optogenetics for investigating functional synaptic communication

Authors: *M. PRAKASH[1], R. LAURENT[4], A. PAL[2], B. W. CONNORS[5], D. LIPSCOMBE[6], J. A. KAUER[7], C. I. MOORE[8], U. HOCHGESCHWENDER[3]
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Abstract: In BioLuminescent driven OptoGenetics (BL-OG) a genetically encoded light source, a luciferase, activates a light-sensing optogenetic element, a channelrhodopsin or a pump. When light emitter and light sensor are tethered, as in luciferase-opsin fusion proteins (luminopsins, LMO), application of luciferase substrate and subsequent light production will change the membrane potential of the cell expressing the LMO. Here we placed the two moieties in pre- and postsynaptic ends of neurons with the goal of achieving BL-OG across the synapse. Neurons isolated from E18 rat cortex were nucleofected either with a pre-synaptically targeted luciferase construct (sbGLuc) or the anion channelrhodopsin iChloC, and were mixed and plated at a 1:1 ratio on 64 electrode 1-well multi-electrode array (MEA) dishes. The above two populations were also individually plated as controls. Silencing of spontaneous neuronal spiking activity through iChloC activation was assessed between DIV 14-21. Blue light (470 nm) from an arc lamp was used to silence iChloC expressing neurons directly, while application of the luciferase substrate coelenterazine (CTZ; final concentration 100μM) was used to silence iChloC expressing neurons across synapses. Assessment of spiking activity showed that for a number of individual electrodes CTZ treatment resulted in a similar pattern of silencing as seen with blue light stimulation. For electrodes that showed similar responses to CTZ treatment and blue light pulses, silencing with CTZ was likely due to trans-synaptic light-activation of iChloC channels. The overall extent of silencing after CTZ application to MEA cultures with mixed populations of luciferase and iChloC expressing neurons was significantly higher compared to cultures of individual populations. Such light activation across synaptic partners, interluminescence, offers the potential to optogenetically dissect synaptic communication in genetically determined neuronal partner populations.

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Poster

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Title: Imaging and regulation of cortical neurons using bioluminescent molecules: A biological method for tracking neural dynamics and driving optogenetic elements in-vivo

Authors: *M. GOMEZ-RAMIREZ[1], A. I. MORE[1], A. PAL[2], B. W. CONNORS[1], J. A. KAUER[1], D. LIPSCOMBE[1], U. HOCHGESCHWENDER[2], C. I. MOORE[1]

[1]Neurosci., Brown Univ., Providence, RI; [2]Neurosci., Central Michigan Univ., Mount Pleasant, MI

Abstract: The development of optogenetics has fostered significant progress in neuroscience by enabling high spatio-temporal control of genetically identified cell populations. Optogenetics is an appealing tool for dissecting neural circuits, and controlling dysfunctional cell ensembles underlying pathological disorders. However, there are several barriers that limit the use of optogenetics in-vivo. In particular, invasive devices used for light delivery (e.g., optical fibers) can be perilous because implants represent a potential path for pathogens to reach the brain. Further, targeting multiple disparate foci can be punitive because it requires inserting several optical fibers that may cause tissue damage. To partly meet these needs, we devised the BioLuminescence-OptoGenetics (BL-OG) method, which leverages bioluminescence (BL) to activate optogenetic elements. In our BL-OG construct, the slow-burn Gaussia luciferase (sbGLuc) is tethered to Volvox-Channelrhodopsin1 (VCHR1), and BL is generated when Coelenterazine (CTZ), the substrate for Gaussia luciferase, is catalyzed by sbGLuc. While we and others have shown that BL-OG can modulate neural activity, there remain major follow-up questions to demonstrate that BL-OG can be a viable strategy for controlling cells' activity in-vivo. Here, we assayed whether BL-OG can be used as a gain modulator by studying whether increases in BL lead to corresponding changes in neural firing. Further, we probed whether BL-OG enhances cells' sensitivity to sensory stimuli, and whether BL-OG can be used to track and dynamically control cells' activity in-vivo. We injected the sbGLuc+VCHR1 construct in mice primary somatosensory cortex (SI), and performed simultaneous BL imaging and electrophysiological recordings while stimulating animals' whiskers prior to and after CTZ injections. Our data revealed a positive relationship between BL and neural firing, and that BL-OG enhanced stimulus-evoked activity of SI neurons. These data indicate that BL-OG systematically regulates cells' activity in-vivo. In a separate set of mice, we injected a calcium-sensitive bioluminescent molecule by splitting the sb-GLuc and linking the components with the calmodulin-M13 peptide sequence. Pilot data revealed increased BL activity during periods of high calcium concentrations. Our data provide evidence that BL-OG can be used to dynamically control the gain of cells in-vivo.

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Poster

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W.M. Keck Foundation

Title: Characterization, sub-cellular targeting and novel applications of a split Gaussia luciferase based genetically encoded calcium indicator

Authors: *A. PAL[1], M. GOMEZ-RAMIREZ[2], W. E. MEDENDORP[1], Z. ZAIDI[1], J. A. KAUER[2], D. LIPSCOMBE[2], B. W. CONNORS[2], C. I. MOORE[2], U. HOCHGESCHWENDER[1]
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Abstract: Calcium (Ca^{2+}) is an essential second messenger that is involved in a multitude of physiological functions ranging from cellular apoptosis to neuronal firing. Therefore, in vivo Ca^{2+} imaging is a very sought after technique. We have split a mutated version of *Gaussi*a luciferase, sbGLuc, known for its high light emission, and introduced the Ca^{2+} sensing moiety Calmodulin-M13 (CaM-M13) between the two split halves, generating Lumicampsin (LMC). In the presence of both Ca^{2+} and the luciferase substrate, coelenterazine (CTZ), the enzyme emits light. Since the dynamics of Ca^{2+} flux vary quite extensively between different organelles and cytoplasmic regions, we have fitted LMC with signaling sequences such that it is localized to various organelles (ER, Golgi, Mitochondria) or is suspended from the inner cell membrane. We transfected HEK293 and Hela cells with these different versions of LMCs and found that they have robust expression, display specific subcellular localization, and faithfully report the calcium dynamics of the site they were localized to. Lastly, LMC reported Ca^{2+} spikes in Hela cells *in vitro* and in mouse barrel cortex *in vivo*.

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Poster

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Title: Chronic activation of dopaminergic neurons via opto-chemogenetics provides neuroprotection in a rodent model of Parkinson's disease

Authors: *F. SHIU[1], K. BERGLUND[2], A. M. FERNANDEZ[1], J. K. TUNG[3], K. MANDI[1], C.-A. N. GUTEKUNST[4], R. E. GROSS[5]
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Abstract: Parkinson's disease (PD) linked to reduced dopamine (DA) levels in the striatum resulted from loss of DA neurons in the substantia nigra (SN). Previous studies have shown neuroprotective effect in physical exercise in rodent models of PD, and people who exercise often have the lowest risk of PD. This neuroprotection may be due to enhanced activity of DA neurons in SN during exercise. In this study, we tested whether increasing activity of DA neurons in the SN could protect them from neurodegeneration induced by 6-hydroxydopamine (6-OHDA) in mice. To increase activity of DA neurons, we used luminopsin, a fusion protein of channelrhodopsin (ChR) and luciferase. Upon application of its substrate coelenterazine (CTZ), the luciferase moiety of luminopsin emits bioluminescence which in turn activate the opsin moiety. To prolong its action for chronic stimulation, we developed a new luminopsin called step-function luminopsin (SFL) based on stabilized step-function opsin (SSFO) and mutated *Gaussia* luciferase which provides blue bioluminescence to SSFO. The SFL gene under control of the human synapsin I promoter was delivered to the SN via unilateral injection of an AAV vector before lesioning the ipsilateral striatum with 6-OHDA. To chronically activate neurons in the SN, CTZ was given daily to the mice for 20 consecutive days starting 5 days before 6-OHDA injection. Unilateral lesioning of DA neurons in the SN resulted in a stereotypical behavior, namely ipsiversive rotations. We assessed this behavior before, 1 week, and 2 weeks after 6-OHDA injections. At the end of experiments, the mice were subjected to immunohistochemistry for DA neurons in the SN. We did not observe a significant difference at any time point between the CTZ group and the control group which received daily injections of vehicle instead. However, there was a significant reduction in rotations from day 7 to day 14 in the CTZ group, but not in the control group. To specifically target DA neurons in SN with SFL, we then repeated the experiments using a conditional expression system, namely transgenic mice expressing Cre recombinase under control of the tyrosine hydroxylase promoter and an AAV vector with the inverted SFL gene and loxP sites. When SFL was specifically expressed in DA neurons in the SN, we observed significantly smaller number of rotations in the CTZ group in day 7 and day14 compared to the control group. These results indicate that neuronal activity of DA neurons provided neuroprotection against 6-OHDA injury and that chronic opto-chemogenetic stimulation with luminopsin could alleviate a symptom in a rodent model of PD.

Disclosures: **F. Shiu:** A. Employment/Salary (full or part-time):; Emory University. **K. Berglund:** A. Employment/Salary (full or part-time):; Emory University. **A.M. Fernandez:** A. Employment/Salary (full or part-time):; Emory University. **J.K. Tung:** None. **K. Mandi:** None. **C.N. Gutekunst:** A. Employment/Salary (full or part-time):; Emory University. **R.E. Gross:** A. Employment/Salary (full or part-time):; Emory University.

Poster

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Title: Optogenetic stimulation and hypoxic preconditioning enhanced wound healing and protection against inflammatory injury

Authors: *Z. Z. WEI[1,2], Y. B. ZHANG[2], J. Y. ZHANG[1], K. I. BURGLUND[3], M. R. MCCRARY[1], J. M. LI[2], L. WEI[1], S. P. YU[1]
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Abstract: Cell transplantation therapy aims to promote tissue repair and functional recovery after brain injury such as ischemic stroke. Transplanted cells, however, may die from a variety of injurious mechanisms in the post-stroke brain. We previously developed a hypoxic preconditioning strategy for enhancing cell survival and the efficacy of stem cell transplantation therapy. Cells with hypoxic preconditioning showed enhanced viability, migration, differentiation, and paracrine potentials. In the present investigation, we explored the application of an optogenetic/chemogenetic approach using cells expressing the light sensitive excitatory channel protein Channelrhodopsin 2 (ChR2) or a bioluminescent luciferase luminopsin 3 (LMO3) and an opsin, Volvox Channelrhodopsin 1 (VChR1). The goal of the study is to enhance activity-dependent therapeutic potentials of transplanted cells. Human HEK293 cells and mouse neural progenitor cells (NPCs) were infected with ChR2 or LMO3-VChR1 virus. Cells were subjected to inflammation triggers including lipopolysaccharides (LPS) and/or oxygen-glucose

deprivation (OGD). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and wound-healing tests showed that co-applied or delayed treatment of optogenetic (10 Hz, 15 min/day) or chemogenetic (1.5 μM coelenterazine, 15 min/day) stimulation increased cell survival and homing to the injury region. We further analyzed the regulation of regenerative factors such as BDNF, SDF-1 and VEGF, and inflammatory/anti-inflammatory genes such as CD16, CD32, CD86, CD11b, TNF-α, IL-1β, CD206, Arg1, Ym1, IL-10 and TGFβ. ELISA assays were performed to measure soluble factors. In conclusion, optogenetic/chemogenetic stimulation may enhance cell therapy by generating an enriched environment with increased regenerative factors and reduced inflammation, which is favorable for cell survival and increased regenerative properties. We also propose that the chemogenetic approach using luciferase-luminopsins can be further developed as a non-invasive strategy to enhance the efficacy and efficiency of stem cell transplantation therapy.

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Poster

717. Optogenetics Methods

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Topic: I.04. Physiological Methods

Support: NIH Grant R44AG046030

Title: Manipulation of sleep activity using optogenetic stimulation

Authors: *D. A. JOHNSON, E. NAYLOR, S. GABBERT, D. V. AILLON, D. A. JOHNSON
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Abstract: The integration of optogenetics and *in vivo* brain responses requires researchers to coordinate disparate tools and timing issues. Standardized techniques and turn-key systems allow researchers to focus on the experiment and not equipment design. Pinnacle's latest system integrates LED optogenetics with EEG and EMG recordings for sleep studies in freely moving mice and rats. In validation experiments using channelrhodopsin-2 transgenic mice, alternating a blue light (445 nm) pulse (10 sec on: 10 sec off) at 40 Hz significantly increased waking activity by 51% while decreasing NREM sleep by 43% and REM sleep by 41% ($p<0.001$) compared to periods with no optical stimulation. This 40 Hz stimulation also increased both frontal (EEG 2) and posterior (EEG 1) gamma activity (25 - 40 Hz). However, a 0.1 Hz pulse protocol only increased gamma activity in the frontal cortex (EEG 2). All experiments used transgenic mice expressing channelrhodopsin 2 in the hippocampus and cortical regions [(Thy1-COP4/EYFP)9Gfng - Jackson Laboratory]. Mice were surgically implanted with two guide

cannulas (BASi, West Lafayette, IN) placed bilaterally in the thalamus along with cortical EEG and intermuscular EMG leads. All surgical procedures were approved by the University of Kansas IACUC. After recovery from surgery (1 wk) blue (445 nm) LED fiber probes were inserted into both cannulas and connected to a head-mounted preamplifier unit. For manipulation of sleep activity, transgenic mice (n=2) were bilaterally stimulated in the thalamic region using either a 0.1 Hz 20 ms stim (pulse protocol) or 40 Hz, 10% duty cycle in alternating 10 second periods (40 Hz protocol). Both protocols were applied in a cycle of 1 hour on 1 hour off for five cycles beginning at 10:00 AM. As a control, the experiment was repeated in the same mice using red (660 nm) LED fiber probes with no changes noted in sleep or gamma activity during periods of stimulation.
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Poster

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Lam Woo Foundation

Croucher Foundation

Title: Optogenetic and pharmacological resting-state functional MRI reveals thalamic modulation of brain-wide functional connectivity

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Abstract: The brain is a highly complex, interconnected structure with parallel and hierarchical networks distributed within and between neural systems. Functional connectivity mapping using resting-state functional MRI (rsfMRI) enables non-invasive visualization of brain-wide networks in humans and animals through coherent infra-slow (<0.1Hz) hemodynamic/BOLD activity. However, the exact underlying neural bases and functional significance remain unclear. Previous studies integrating large-scale electrical or Ca^{2+} recordings imply that slow, oscillating neural activity (<1Hz) constraints and elicits these rsfMRI BOLD activities. This indicates that interrogating the brain's underlying electrical activity can provide mechanistic insights into brain-wide rsfMRI connectivity. Numerous long-range networks exist, subserving the functions of particular systems and their interactions. One classical example is the thalamo-cortical-thalamic network, which interconnects the thalamus and neocortex via thalamo-cortical and cortico-thalamic projections. In this study, we optogenetically stimulate ventral posteromedial thalamus (VPM) thalamocortical excitatory neurons and pharmacologically inactivate VPM thalamocortical neurons, to investigate whether modulating and/or disrupting the neural activity of such an integral brain network could uncover the neural bases of rsfMRI. Optogenetic control of VPM thalamocortical excitatory neurons in adult male Sprague-Dawley rats was enabled through AAV5-CaMKIIα-ChR2(H134R). RsfMRI scans were performed before, during (i.e., 1Hz, 473nm, 10% duty cycle, 40mW/mm^2) and after optogenetic stimulation. Inactivation of VPM was enabled through the use of Tetrodotoxin (TTX; 5ul, 5ng/uL). Our results demonstrated that optogenetic excitation of the VPM thalamocortical excitatory neurons at 1Hz enhanced brain-wide rsfMRI connectivity, specifically somatosensory, visual and auditory networks, whereas, TTX inactivation of VPM decreased rsfMRI connectivity. Spectral analysis indicated that such changes were underpinned by neuromodulatory effects on the infra-slow rsfMRI BOLD activity. Our study suggests that 1Hz optogenetic stimulation of VPM initiates slow oscillations that may couple with infra-slow oscillations, leading to enhanced rsfMRI connectivity. Whereas, TTX inactivation of VPM disrupts the initiation or propagation of these oscillations, decreasing rsfMRI connectivity. By manipulating the specific activities within the thalamo-cortical-thalamic network, optogenetic rsfMRI presents a powerful approach to dissect the neural bases of rsfMRI connectivity.

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Poster

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Charles and Ann Sanders MGH Research Scholar Award (R.T.P.)

Title: A high-conductance chemo-optogenetic system based on the vertebrate channel Trpa1b

Authors: *P. LAM[1], S. K. MENDU[2], R. W. MILLS[3], B. ZHENG[3], H. PADILLA[1], D. J. MILAN[3], B. N. DESAI[2], R. T. PETERSON[1]
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Abstract: Optogenetics is a powerful research approach that allows localized electrical modulation of selected cells within an animal via the expression of genetically encoded photo-excitable ion channels. Commonly used optogentic techniques rely on the expression of microbial opsin variants, which have many excellent features but suffer from various degrees of blue spectral overlap and limited channel conductance. Here, we expand the optogenetics toolbox in the form of a tunable, high-conductance vertebrate cation channel, zTrpa1b, coupled with photo-activated channel ligands, such as optovin and 4g6. Our results demonstrate that zTrpa1b/ligand pairing offers high light sensitivity, millisecond-scale response latency, as well as adjustable channel off latency. Exogenous *in vivo* expression of zTrpa1b in sensory neurons allowed subcellular photo-activation, enabling light-dependent motor control. zTrpa1b/ligand was also suitable for cardiomyocyte pacing, as shown in experiments performed on zebrafish hearts *in vivo* as well as in human stem cell-derived cardiomyocytes *in vitro*. Therefore, zTrpa1b/optovin represents a novel tool for flexible, high-conductance optogenetics.

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Poster

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L Sileo, M De Vittorio, B Sabatini - NIH 1 U01 NS094190-01

Title: Tapered optical fibers for optogenetics

Authors: *F. PISANO[1], G. MANDELBAUM[2], M. PISANELLO[1], I. A. OLDENBURG[2], L. SILEO[1], J. E. MARKOWITZ[2], R. E. PETERSON[3], A. DELLA PATRIA[1], R. PEIXOTO[4], T. M. HAYNES[2], E. MAGLIE[5], M. S. EMARA[5], E. BELLISTRI[1], B. SPAGNOLO[1], E. LEMMA[5], A. RIZZO[5], S. R. DATTA[3], B. L. SABATINI[2], M. DE VITTORIO[6], F. PISANELLO[1]
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Abstract: Tapered optical fibers (TF) recently emerged as an important complement to existing light- delivery methods for in vivo optogenetics [1,2,3]. Here we review our recent advancements in the fabrication, development and *in vivo* use of these devices towards spatio-temporal control and simultaneous extracellular readout of neural activity.
We used TFs with a low taper angle (<4°) to obtain dynamically reconfigurable light delivery over neural structures extending from ~0.5 mm to 2 mm. The exploitation of mode division de-multiplexing properties of the fiber taper allows for two operation modalities:(i)uniform illumination of wide neural volumes obtained by injecting light within the fiber full numerical aperture [1]; (ii) spatial subsampling of the region of interest with a selectivity of a few hundreds of micrometers in the dorso-ventral direction obtained by changing the light coupling angle at the fiber input [1]. Light delivery volumes can also be confined to a few tens of micrometers by opening small optical windows on a light-shielding metal layer deposited all around the taper [2,3]. These small excitation spots, obtained by Focused Ion Beam milling or by direct laser writing, can be selectively activated by changing the light input angle [2,3].
When compared with bare TFs, this latter fabrication approach offers additional flexibility in the geometrical design of light-emitting regions, as light output can be tailored to experimental demands. For example, layer-selective light-delivery can be targeted to cortical sub-regions by fabricating ring-shaped windows around the taper. Metallized TF devices can also be empowered with further micro-fabrication processing. This allowed us to realize micro-electrodes for extracellular recording next to light-delivery spots. This was done by coating the taper with multiple metal layers that were mutually insulated by interfacing each metal surface with a parylene-c deposition. Platinum electrodes were then fabricated in milled recesses of the metal surfaces by Ion Beam Induced Deposition. These electrodes, that have impedances comparable to commercial devices, can successfully record single unit activity and LFPs signals *in vivo*. All these devices have been tested *in vivo* in both head- restrained and free moving mice.
[1] Pisanello F, et al Biorxiv 094524 (2016)
[2] Pisanello F, et al Neuron 82, 1245-1254 (2014).
[3] Pisanello M, et al Biomed Opt Express 6, 4014 (2015).

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Poster

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Marie Curie Individual Fellowship, 747598 — 3DMUCHO — H2020-MSCA-IF-2016/H2020-MSCA-IF-2016

Title: Parallel optical method enables submillisecond optogenetic activation in mouse visual cortex *In vivo*

Authors: *I.-W. CHEN[1], E. RONZITTI[1], O. A. SHEMESH[2], D. DALKARA[4], H. ZENG[5], E. S. BOYDEN[3], V. EMILIANI[1], E. PAPAGIAKOUMOU[1]
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Abstract: The ability to control the excitability of a neuronal sub-population with high spatiotemporal precision and resolution is desirable for dissecting circuit mechanisms underlying perception or behaviour. Optogenetics makes such selective manipulation feasible by combining the suitable optical method to activate or inactivate neurons that are genetically encoded with light-sensitive opsins. Two-photon (2P) parallel light-patterning with phase modulation is an effective approach to actuate opsins expressed in neurons situated deeper in the brain with enhanced temporal resolution. Here, we propose an optical system using computer-generated holography and temporal focusing for 2P optogenetic activation. Combined with an amplified laser (emission wavelength λ=1030 nm, maximum output pulse energy 20 μJ, maximum average power 10 W) our system achieves suprathreshold activation with a localized holographic spot (12 μm in diameter, 10 μm Full Width at Half Maximum optical axial resolution) of low illumination power density (0.1-0.2 mW/μm^2) and short light-pulses (2-15 ms) in layer 2/3 neurons of anesthetized mouse visual cortex *in vivo*. Using 2P-guided whole-cell or cell-attached recordings, we found that positive neurons expressing either of the three opsins, ReaChR, CoChR, or ChrimsonR, elicit spikes of small peak latencies and sub-millisecond jittering. In addition, trains of action potentials were induced in positive neurons following repetitive light-pulses up to tens of Hz. Our optical system for 2P holographic photostimulation is advantageous for altering presynaptic inputs in identifying neuronal connections. Further, it can be flexibly

combined with functional imaging methods for all-optical investigation of specific circuit dynamics.

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Poster

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Marie Sklodowska-Curie IF, 746598 — ME-Optogen — H2020-MSCA-IF-2016/H2020-MSCA-IF-2016

Title: Three-dimensional, high-resolution, parallel patterned illumination via multiplexed spatiotemporal wavefront shaping

Authors: E. PAPAGIAKOUMOU, N. ACCANTO, C. MOLINIER, D. TANESE, *E. RONZITTI, I.-W. CHEN, V. EMILIANI
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Abstract: In the past ten years, optogenetics has been established as the key method to control the activity of specific neuronal populations using light. A major challenge is to develop innovative optical tools to target individual neurons that are distributed in three dimensions (3D) in the brain, at high spatiotemporal resolution and precision. In pioneering experiments using phase modulation methods, such as Computer-Generated Holography (CGH), in combination with temporal focusing (TF), we have demonstrated the generation of arbitrary light excitation patterns with preserved axial resolution and used this approach for neuronal activation in brain slices. Most recently, we have extended this method to the generation of spatiotemporally focused patterns at axially distinct planes by demonstrating a new configuration based on the use of two spatial light modulators (SLMs) that can jointly translate single or multiple temporally focused holographic targets. This strategy, however, was intrinsically limited to few axial planes. Here, we propose a novel optical system overcoming this limitation and capable of simultaneous

generation of hundreds of illumination targets arbitrarily arranged in 3D, with an axial resolution decoupled from the lateral size. The scheme comprises: i) a phase SLM to create a user defined two-dimensional shape, ii) a diffraction grating, placed at the image plane of the SLM to perform temporal focusing, and iii) a second SLM placed after the grating to generate multiple replicates of the original shape at distinct lateral and axial positions. The number of available replicas is now only limited by the number of illuminated pixels at the second SLM, which, compared to previous techniques, provides an increase of at least one order of magnitude in the number of different planes that can be simultaneously addressed at the sample position.
We demonstrate parallel projection of at least 50 high-resolution spots of 15 μm diameter in a volume of 300x300x500 μm^3. Finally, by combining the system with high-power Ytterbium fiber laser systems, we demonstrate that the power available at each replicated spot enables *in vivo* optogenetics control of neuronal activity in layer 2/3 of anesthetized mouse visual cortex.
The approach proposed here for performing 3D photostimulation with single neuron spatial resolution combined with two-photon excitation imaging opens the way for all-optical manipulation of neural circuits with unprecedented spatiotemporal specificity.

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Poster

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Support: NIH 1-U01-NS090501-01

Title: Probing the retinal circuit by combining two photon holographic stimulation and multi electrode recordings

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Abstract: A major purpose of sensory neuroscience is to understand how a neural circuit generates complex activity patterns in response to sensory stimuli. While recent works have

made possible to access the full connectome of a neural circuit, there is still a gap between its detailed anatomical reconstruction, and the functional characterization of its neural responses. To bridge this gap, we need to understand how the perturbation of each neuron will influence the activity of the circuit, and reconstruct the complete functional connectivity diagram.
The retina transforms the visual scene in spikes and transfers them to the brain. Photoreceptors transduce light into electrical currents, bipolar cells process this signal and transmit it to ganglion cells, which send spikes to the brain A key component of retinal processing is the information transfer from the intermediate bipolar cell layer to the ganglion cell layer. Our understanding of this transfer is limited: while multi-electrode arrays allow recording large populations of ganglion cells, bipolar cells cannot be easily recorded or stimulated in the intact retinal circuit Here we present a novel method where we combined several techniques to record ganglion cells with multi-electrode arrays while perturbing individual bipolar cells using optical and optogenetic tools. We used an AAV and a specific promoter to express light sensitive proteins selectively in rod bipolar cells. We then used 2 photon computer generated holography, a technique to pattern light to stimulate individual neurons, while simultaneously recording ganglion cells with a multi-electrode array. Thanks to this combination of optical and electrophysiological tools, we could stimulate selectively rod bipolar cells and record the impact of this stimulation on the spiking activity of ganglion cells. Our method also allowed us to stimulate several bipolar cells simultaneously to measure the impact of complex stimulation patterns on the ganglion cell layer.
We are currently using this technique to understand how each type of ganglion cell is modulated by rod bipolar cells. This method allows a precise probing of the retinal circuit and paves the way towards complete functional connectomics of the retina

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Poster

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Title: Widespread functional opsin transduction in the rat cortex via convection-enhanced delivery

Authors: *Z. YU[1], I. OZDEN[1,2], A. V. NURMIKKO[1]
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Abstract: For studies on the functions of the cortex, a planar structure with distributed functional regions, spatially and temporally controlled optogenetic perturbations require opsin expressions over widespread areas. However widespread opsin expression in the cortex of rats, where transgenic models for optogenetics have not been established, is not practical to achieve with the traditional diffusion-based virus transduction methods (DBD).
Here we report protocols developed for convection-enhanced delivery (CED) of virus for optogenetic transduction in the cortex of rats. Targeting the motor forelimb area as an example, we performed dual-site CED (6 μL of virus per site, 3 mm distance between sites) in the rat motor cortex.
We demonstrated widespread opsin expression over large cortical area (8.2 ± 1.4 mm in the AP direction, 4.9 ± 0.4 mm in the ML direction, N = 7 rats). Compared with the conventional DBD method, we achieved about 160-fold increase in the volume and 60-fold increase in the cross-sectional area of opsin expression. The total injection time was also reduced by at least 10 times, if similar spatial extent of expression were to be achieved with the DBD method. The optogenetic transduction was functionally robust that both optical modulation of neuronal activity and elicitation of overt motor responses were reliably observed. Around the site of each CED infusion, a region of diminished opsin expression was commonly found (0.43 ± 0.10 mm in diameter). While we were unable to rule out the possibility of tissue damage due to high infusion rates, we did not find significant reduction in neuronal population density (NeuN) or increase in astroglial scarring (GFAP) in the vicinity of the injection site. However, to minimize the influence of the potential confounding factors due to damages at the injection sites, we purposefully chose to perform the dual-site injection at the perimeter of the region-of-interest. We believe that the adaptation of CED technique to rat cortex, as introduced here, will not only benefit optogenetics studies, but also others where widespread cortical coverage is required.

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Poster

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Title: Channelrhodopsin-2 expression localized to deep CA1 hippocampal sublayer in Thy1 line 18 mice

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Abstract: Optogenetic techniques have greatly advanced our ability to assess neural circuitry. The use of transgenic animals has allowed for increased precision with these techniques. The Thy1-ChR2 transgenic mouse is among the most commonly used transgenic optogenetic lines. The Thy1 promoter is developmentally expressed resulting in variable expression patterns between (but not within) founder lines. The expression patterns of ChR2 in the various founder lines have been characterized generally, but detailed cell-specificity has not yet been examined. An understanding of such expression can allow for a more robust interpretation of experimental results when using these optogenetic techniques. To address this need we compared expression of ChR2 in founder line 18, to expression profiles of cell specific markers in CA1 of the hippocampus using immunohistochemistry. Neurons expressing ChR2 were localized to the deep calbindin-negative sublayer of CA1 and were not colocalized with calbindin (R=0.054 +/- 0.030, n=15) or parvalbumin (R=0.200 +/- 0.041, n=14) expressing interneurons. These results highlight the utility of Thy1-ChR2-YFP line 18 mice to examine the functional role of excitatory neurons in deep CA1 pyramidal cell sublayer. These mice represent the first example of specific expression in this cell-type and should serve as a powerful model for those studying hippocampal microcircuitry.

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Poster

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NIH (1U01NS090576-01)

Title: Optical manipulation of neural activity with cellular resolution *In vivo*

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Abstract: Sensory information is encoded within the brain in the form of distributed spatial and temporal patterns of neuronal activity. To causally test which specific features of the sensory stimulus are encoded by these activity patterns and how this information is used to drive behavior, we need a method to perturb with single-cell resolution the activity of the multiple cell types that are engaged in sensory processing. To this goal, we combined two-photon digital holography using liquid crystal spatial light modulators to control the size and shape of the two-photon excitation volume (patterned illumination) with viral delivery of channelrhodopsin-2 (ChR2) in various cellular populations of the mouse somatosensory cortex. We validated our approach performing juxtasomal electrophysiological recordings from ChR2-positive cells during patterned illumination of their cell-body with extended shapes in anesthetized animals. Despite differences in input resistance and membrane conductance, we found that layer II/III principal neurons, parvalbumin-positive interneurons, somatostatin-positive cells, and layer IV excitatory neurons all significantly increased their firing rate in response to patterned illumination. The firing probability during patterned illumination increased with stimulation power and moving the excitation volume away from the cell body in the radial or axial directions decreased stimulation efficiency with cell-type specific spatial constants. Ongoing efforts are focused on applying patterned illumination in awake mice, in order to investigate how the concerted activity of single neurons contributes to network function and behavior.

Disclosures: A. Forli: None. **N. Binini:** None. **D. Vecchia:** None. **S. Bovetti:** None. **C. Moretti:** None. **T. Fellin:** None.

Poster

717. Optogenetics Methods

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 717.25/VV57

Topic: I.04. Physiological Methods

Support: KAKENHI Grant 26293046

KAKENHI Grant 26640041

KAKENHI Grant 16H01271

KAKENHI Grant 15H01428

CREST JST Grant JPMJCR1656

Title: Fiberless optogenetics to manipulate neuronal activity in both *Ex vivo* and *In vivo*

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Abstract: Brains exert their functions by forming complex neuronal networks. Last decades, optogenetics emerges as a powerful tool to decipher neuronal basis underlying intricate behaviors. However, the conventional optogenetics method requires optical fiber insertion due to low tissue permeability of visible light. It causes tissue damage and behavioral restriction. To address these problems, we developed a noble technique to manipulate neurons by using near-infrared light (NIR) which has high tissue permeability. Here, we used lanthanide-based up-conversion, which convert long wavelength NIR to shorter wavelength of visible light. This fiberless optogenetics allows us to manipulate neuronal activity in both *ex vivo* and *in vivo*. We first expressed three different channelrhodopsins: ChR2, C1V1, and ChrimsonR in HEK293 cells and recorded membrane current at holding potential of -60 mV. Cover glass containing HEK293 cells were placed on the sheet containing lanthanide (20 mg/ml). NIR was then illuminated through the objective lens. Lanthanide, NaYF4:Yb/Er, which converts NIR (976 nm) to green light (540 nm) generated the largest membrane current on HEK293 cell expressing C1V1. We next studied the permeability of NIR in mice brain, skull, and skin. We targeted two different brain area, the dorsal striatum (dSTR, ~2.0 mm depth from brain surface) and medial prefrontal cortex (mPFC, ~1.5 mm depth from brain surface). Adeno-associated virus vector containing gene to express C1V1 was infected in the dSTR or mPFC of mice brain. Brain slice recording on the lanthanide sheet confirmed that NIR can depolarize and induce firing in C1V1 expressing dSTR and mPFC neurons. Next, lanthanide particles (20 mg/ml) were injected in the same brain area expressing C1V1. NIR illumination induced increased locomotor activity in these mice. However, NIR itself did not induce increased locomotor activity in lanthanide alone or C1V1 alone injected mice, suggesting that up-conversion light emitted from lanthanide activated neighboring neurons expressing C1V1 *in vivo*. These data represented the feasibility of fiberless optogenetics in freely behaving mice.

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Poster

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Topic: I.04. Physiological Methods

Support: Pisanello F, Pisano F, Bellistri E, Maglie E European Research Council (Project MODEM, Starting Grant, GA #677683)

L Sileo, M De Vittorio NIH 1 U01 NS09419001

Title: Tapered optical fibers as potential tools to reduce heating artifacts in optogenetics experiments

Authors: *E. BELLISTRI[1], M. PISANELLO[1], E. MAGLIE[1], F. PISANO[1], B. SPAGNOLO[1], L. SILEO[1], G. MANDELBAUM[2], M. DE VITTORIO[1], F. PISANELLO[1]
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Abstract: Optogenetics is a powerful method to control brain activity with light, and therefore to create detailed maps and models of brain circuitry. However, some very recent studies pointed out possible adverse effects of heating induced by tissue illumination, including tissue damage, spiking rate increase and fMRI artifacts due to light-driven vasodilation [1, 2]. Here we show that tapered optical fibers (TF) with a low taper angle [3] can be used to deliver light in wider brain volumes with reduced heat gradients with respect to flat fibers (FF) commonly used to deliver light into the brain. We modeled light intensity from TFs as single photons emitted with an angle with respect to the fiber axis and at specific positions along the taper, as retrieved by experiments and ray tracing simulation. These data were used as initial condition in a Monte Carlo simulation [2] that, based on tissue absorption and scattering parameters, allowed estimate the temperature increase affecting cells around the fiber. The code also returns the estimated light intensity distribution around the taper, allowing for a comparison with experimental data and used as a control simulation to assure the reliability of the implemented algorithm. We simulated three different types of tapered fiber with Numerical Apertures 0.22, 0.39 and 0.66 and taper angles 2.2°, 2.9°, 4° that allow homogeneous light delivery in dorso-ventral structures extending ~750 μm, ~1300 μm and ~1800 μm, respectively. When delivering a total of 5mW at 473nm into the brain, this resulted in an illuminated volume with powers >1mW/mm^2 of 330430 μm^3, 358130 μm^3, 389590 μm^3 with temperature gradients of 1.14°C, 0.85°C and 0.65°C for the 0.22, 0.39 and 0.66 TF. For the same light power, a FF with 200/225um core/cladding diameters allows light delivery >1mW/mm^2 on a volume of of 84000 μm^3 with a heat gradient of 2.5°C. A similar trend was observed at red-shifted wavelengths (560nm), although the illuminated volume increases and the temperature gradient decreases for both FFs and TFs. In summary, we suggest that tapered optical fibers can be used to obtain wider brain stimulation with lower temperature increase and smaller heat gradients with respect to flat-cleaved fibers.
[1] Rungta RL, Osmanski B-F, Boido D, Tanter M, Charpak S. Light controls cerebral blood flow in naive animals. *Nature Communications*. 2017.
[2] Stujenske JM, Spellman T, Gordon JA. Modeling the spatiotemporal dynamics of light and heat propagation for *in vivo* optogenetics. *Cell reports*. 2015.
[3] Pisanello F, Sileo L, Oldenburg IA, et al. Multipoint emitting optical fibers for spatially addressable in-vivo optogenetics. *Neuron*. 2014.

Disclosures: E. Bellistri: None. **M. Pisanello:** None. **E. Maglie:** None. **F. Pisano:** None. **B. Spagnolo:** None. **L. Sileo:** None. **G. Mandelbaum:** None. **M. De Vittorio:** None. **F. Pisanello:** None.

Poster

717. Optogenetics Methods

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Topic: I.04. Physiological Methods

Support: NIH Grant R21EY027588

Title: Extending optical techniques to deep brain regions through minimally invasive, splaying optical microfibers

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Abstract: Rapidly advancing optical techniques for recording from and manipulating neural activity have been constrained to more superficial brain regions due to light scattering. Developments in multiphoton microscopy have enabled recording up to 1mm below the surface, while implants, such as GRIN lenses and microprisms have expanded the reach of optical techniques, but with costs in terms of constrained, head-fixed recording paradigms and tissue damage at and around the implant.

Based on the principles of fiber photometry, we have developed implantable bundles of hundreds or thousands of optical microfibers, with diameters between 6μm and 8μm. During insertion, each fiber moves independently, following a path of least resistance and splaying through the target region. The small cross section of each fiber minimizes both neuronal damage and tissue response. Previously shared histology from implants in the zebra finch basal ganglia (depth of 2.9mm) showed consistent splay with an average distance of 22.9μm between neighboring fibers; immunohistochemical staining after chronic implants (3+ months) revealed neurons in close proximity to the fibers, indicative of minimal tissue damage.

The fibers exhibit total internal reflection due to the difference in the refractive index between the core (4.4μm diameter) and the cladding, enabling each fiber to bidirectionally interface with a small volume of neurons near the tip (an average of 2.8 projection neurons in the 18,000μm^3 volume that is accessible [>0.1 normalized fluence] to each fiber). The fibers have the potential to collect fluorescent traces from genetically encoded calcium or voltage indicators, as well as to stimulate opsins.

At our poster, we will present efforts to record calcium traces via the optical microfibers from the zebra finch basal ganglia and evaluate these efforts against a model of the underlying optics and mixing process that takes place as a result of the incoherent splaying of the fibers during insertion. From the model and from these initial recordings, we plan to estimate the distribution of signals reaching each fiber and how this linear mixing process can be reversed.

These initial recordings demonstrate the feasibility of using optical microfibers to extend the

powerful suite of optical techniques to previously inaccessible deep brain regions, providing a minimally invasive, bidirectional, multichannel interface for reading and modifying neural activity.

Disclosures: **N. Perkins:** None. **D. Semu:** None. **J. Shen:** None. **T.J. Gardner:** None.

Poster

717. Optogenetics Methods

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Support: NINDS Grant R01NS42402

DIBTH0632

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NCCAM Grant R21AT001607

Title: Optogenetic and chemogenetic inhibition of striatal dopaminergic cell transplants in hemiparkinsonian rats to ameliorate graft-induced dyskinesias

Authors: ***V. IYER**[1], K. VENKITESWARAN[2], N. PATEL[2], S. CHINNIAH[2], K. LE[2], C. WHITE[2], E. HANDLY[2], A. ZENEROVITZ[2], A. COCKING[3], Z. LIU[3], C. RAMAKRISHNAN[4], K. DEISSEROTH[4], T. SUBRAMANIAN[2]
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Abstract: Striatal fetal ventral mesencephalic (FVM) transplants are under investigation again after a period of moratorium as an experimental therapy in Parkinson's disease (PD) patients. However, a concern with FVM transplants is the risk of developing disabling graft-induced dyskinesias (GID). We tested the therapeutic efficacy of optogenetic and chemogenetic inhibition to overcome GID without losing the anti-parkinsonian benefits of striatal xenotransplantation. Adult SD rats were unilaterally lesioned to cause stable hemiparkinsonism (HP) as determined by a behavioral battery of tests (BBT). The denervated striatum was injected with AAV2-Ef1a-mCherry-IRES-WGA-Cre three weeks prior to transplantation. In separate experiments, single cell suspension of E13.5 mouse FVM tissue was transfected with either

AAV5-Ef1a-DIO-eNpHR3.0-EYFP or AAV8-hSyn-DIO-hM4Di-mCherry in vitro prior to stereotactic transplantation into the striatum. Thus, synaptic connectivity between the graft and the host was obligate for the expression of eNpHR3.0-EYFP or hM4Di-mCherry in these separate groups of grafted animals. Activation of eNpHR3.0 using a 590nm light source (5mW) or the administration of the DREADD activator clozapine-N-oxide to activate hM4Di caused a complete loss of graft derived behavioral benefits (Vibrissae evoked forelimb placement test; $p<0.05$) that was completely reversible. Control experiments did not produce any loss of beneficial behavioral effects. The 5-HT6 receptor agonist ST1936 induced GID that was significantly ameliorated by both optogenetic and chemogenetic inhibition (dyskinesia score; $p<0.05$) without any loss of graft derived benefits. All grafted animals had excellent survival of FVM dopaminergic neurons that demonstrated mature expression of tyrosine hydroxylase (TH) positive axonal projections. Grafted neurons that were eNpHR/EYFP/TH positive or hM4Di/mCherry/TH positive were noted to make synaptic connections with host medium spiny neurons. Microdialysis levels of dopamine, 5HT-6 receptor expression and serotonin transporter levels were also assessed. We show that functional synaptic connectivity between the graft and the host striatum is critical for anti-parkinsonian behavioral benefits from FVM cell transplantation and that ST-1936 induced GID can be markedly ameliorated without loss of graft function using chloride mediated hyperpolarization or by DREADD mediated GPCR inhibition. Our findings suggest that ionic and GPCR modulation are effective to control 5-HT6 receptor mediated GID and provide pre-clinical proof of principle for the use of optogenetic or chemogenetic inhibition to treat GID in PD.

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Poster

717. Optogenetics Methods

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Title: Novel luminopsins for improved bimodal opto- and chemogenetic control of neural function

Authors: *S. PARK[1,2], S.-H. SONG[3,4], B. PALMATEER[5,6], A. PAL[5,6], G. P. SHALL[5], R. M. WELCHKO[5], K. IBATA[7,8], A. MIYAWAKI[7], G. J. AUGUSTINE[1,3,4], U. HOCHGESCHWENDER[5,6]
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Abstract: Bioluminescence-driven optogenetics can be useful for bimodal opto- and chemogenetic control of neural activity, including both neuronal activation and silencing. Luminopsins (LMOs), which are composed of an opsin fused to a luciferase, have proven to be versatile tools for controlling neuronal activity and interrogating neuronal circuits (PLoS ONE 8: e59759; PNAS 113: E358). Here we have expanded the luminopsin tool kit by fusing a new version of *Gaussia* luciferase (GLuc) with high light-emission, GLucM23, to depolarizing and hyperpolarizing channelrhodopsins with increased light sensitivity. The combination of GLucM23 with *Volvox* channelrhodopsin-1, VChR1, produced LMO4, while combining GLucM23 with the anion channelrhodopsin, iChloC, yielded iLMO4. The efficacy of bioluminescence-driven optogenetic activation and silencing was evaluated by whole-cell patch-clamp recordings and multi-electrode array recordings in cultured neurons. Both luminopsins proved very efficient in activating and silencing neurons upon exposure to the luciferase substrate, coelenterazine (CTZ), to generate light emission mediated by GLucM23. The coupling efficiency - a measure of the ability of light generated by GLuc to activate the channelrhodopsins - was higher for LMO4 and iLMO4 than for all previous luminopsins. Moreover, these new LMOs very efficiently controlled neuronal activity *in vivo*, as indicated by the ability of injected CTZ to alter amphetamine-induced rotations in rats. We conclude that LMO4 and iLMO4 are novel and effective tools that improve bimodal opto- and chemogenetic control of neuronal activity and brain function, from single-cell to behavioral levels.

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Poster

717. Optogenetics Methods

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Program#/Poster#: 717.30/VV62

Topic: I.04. Physiological Methods

Support: NINDS Brain Initiative Grant U01NS090590

Title: Optogenetic control of BDNF/TrkB signalling

Authors: *A. M. ZBELA, D. A. GELL, L. C. FOA, J. Y. LIN
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Abstract: Brain-derived neurotrophic factor (BDNF) and its receptor, receptor tyrosine kinase B (TrkB), are involved in many forms of neuronal plasticity and are thought to be associated with functional and structural long-term potentiation (Minichiello et al., 2002, Harward et al., 2016). Nevertheless, a precise molecular mechanism of TrkB activity in synaptic plasticity as well as its role in learning and memory formation in behaving animals is still elusive. To address the question how distinct downstream signalling pathways of TrkB control neuronal plasticity and how these mechanisms in specific cells can affect learning and memory formation, we developed an optogenetic approach to activate TrkB signalling independently of BDNF. We utilized a membrane recruitment strategy with the light-induced photodimerizer CRY2/CIB1 in combination with the kinase domain of TrkB to activate the corresponding signalling pathway. In HEK293 cells expressing the engineered proteins, light illumination leads to elevated intracellular calcium, consistent with the activation of phospholipase Cγ (PLCγ) which is known to be associated with TrkB signalling. Moreover, the preliminary results showed that light also triggers the mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and Akt kinase pathways. By generating mutant variants of the kinase domain, we are able to recruit one signalling cascade over others with our optogenetic approach, leading to the biochemical dissection of the pathways. This tool is currently being validated in cultured neurons and will be further utilized to investigate the roles of BDNF/TrkB signalling in synaptic plasticity.

Disclosures: **A.M. Zbela:** None. **D.A. Gell:** None. **L.C. Foa:** None. **J.Y. Lin:** None.

Poster

718. Clinical Computational Models

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Program#/Poster#: 718.01/VV63

Topic: I.06. Computation, Modeling, and Simulation

Support: HU0001-15-2-0024

Title: Examination of PTSD pathology using small world graph representations

Authors: *J. K. STATZ[1,2], R. M. MCCARRON[1,3], E. MCGINNIS[4], M. L. MEHALICK[1], S. T. AHLERS[1], P. B. WALKER[1], I. N. DAVIDSON[4], J. D. HUGHES[5]
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Abstract: Previous research using functional imaging has shown that graphs constructed from these data sets demonstrate small world properties, with resting-state connectivity characterized by short path lengths and high clustering coefficients (Spoorns et al, 2000). Alteration of these properties in a network may indicate neurological dysfunction (Liu et al, 2008; Micheloyannis et al, 2006). The results of comparing these small world connectivity measures, as well as new measures and analysis methods, between a post-traumatic stress disorder group and a normal group will be presented and discussed. The dataset is the Alzheimer's Disease Neuroimaging Initiative Department of Defense. The data is represented by a graph G and consists of the nodes V, the edges that connect these nodes, and the weights of the edges that represent the distance or similarity of the two connected nodes. These graphs can be represented using the adjacency matrix A, where for nodes i and j, $A_{i,j}$ describes the edge connecting the nodes. Here the nodes are the AAL regions and edges are determined by the thresholded absolute Pearson correlation of the BOLD signals over time. The two common measures for describing the small-world properties of a graph are: average characteristic path length, which is the mean of all shortest path lengths for all node pairs; and average clustering coefficient, the mean of the individual clustering coefficients of each node, describing how connected a node is to each of its connected neighbors. In addition to these, other measures that may provide insight are: average max flow, which uses the edge weights to determine the max flow from one node to another via non-overlapping (disjointed) paths; and expected commute time, the time necessary for a random walker to travel from node i to j and back. New methods of analysis include: component analysis, which examines the size and number of connected components and common dropouts (components of size three or less) between groups; and spectral graph theory, examining the eigenvectors and eigenvalues of the graph. It was found that, on average, the PTSD cohort had a shorter characteristic path length, higher average clustering coefficient, and higher average max

flow than the control group; these observations lead to the conclusion that PTSD graphs are more connected. Examination of the mean Pearson correlations of the PTSD and control groups supports this, with the PTSD mean correlation the higher of the two, and even at lower thresholds for sparsifying the graph *G*, the control graph was much sparser. Also, low dropout overlap within the PTSD cohort during component analysis suggests that there is high variation in PTSD network structure.

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Poster

718. Clinical Computational Models

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Topic: I.06. Computation, Modeling, and Simulation

Support: FNR-AFR PhD grant 10099424

Title: Neuronal hyperactivity in LRRK2 G2019S cellular models of Parkinson's Disease

Authors: *S. HACHI[1], E. LUCUMI MORENO[1], J. C. SCHWAMBORN[1], P. VANDEN BERGHE[2], R. M. T. FLEMING[1]
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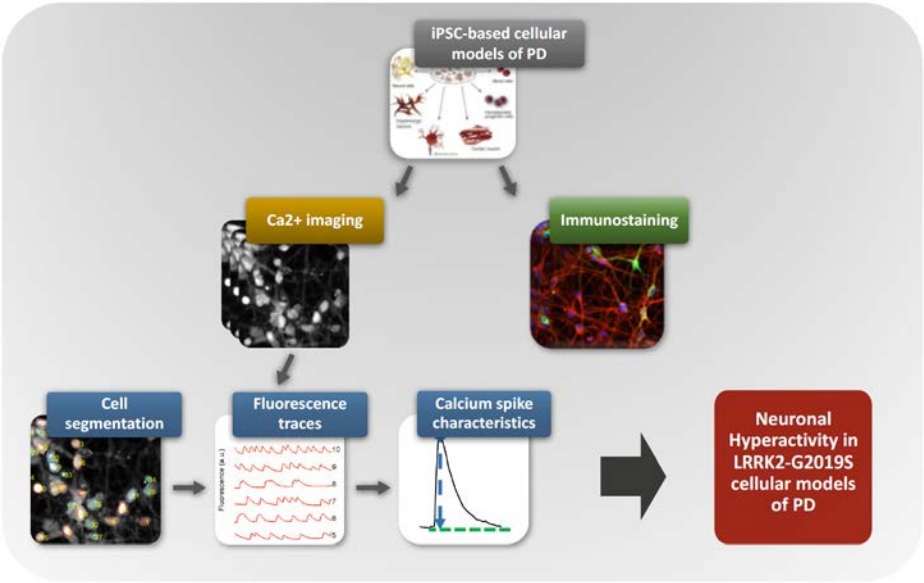
Abstract: Parkinson’s disease (PD) is the second most common neurondegenerative disease affecting more than 10 million people worldwide. Monogenic forms of PD are associated with mutations in various genes, including the gene encoding the leucine-rich repeat kinase 2 (LRRK2). Even though extensive investigations have been carried out to elucidate the function of this enzyme, it is still incompletely understood. Several studies have reported the effect of LRRK2-G2019S mutation on neurite branching, calcium hometostasis and mitochondrial function. However, less is known about its implication on neuronal activity. To investigate whether LRRK2-G2019S mutation alters neur- onal activity, we combined different state-of-the-art technologies including induced pluripotent stem cells (iPSCs), calcium imaging and computational image analysis. We used human neuroepithelial stem cell-derived neurons ob- tained from iPSCs as cellular models of PD. We monitored the spontaneous activity of these neurons carriyng a LRRK2-G2019S mutation using Fluo4-based calcium imaging. To analyse the calcium imaging data, we implemen- ted a fully automated image analysis pipeline that integrates automated neuronal segmentation, calcium transient measurement and transient property quantification such as inter-spike interval, spike amplitude and spike width. Interestingly, a shortening of inter-spike intervals was observed in neurons carrying a LRRK2-

G2019S mutation compared with controls. This corresponds to an increase in the rate of spontaneous calcium transients induced by action potentials. Thus, our findings suggest that this LRRK2 mutant alters the spontaneous activity of neuronal populations inducing hyperactivity in cellular models of PD.
1



Disclosures: **S. Hachi:** None. **E. Lucumi Moreno:** None. **J.C. Schwamborn:** None. **P. Vanden Berghe:** None. **R.M.T. Fleming:** None.

Poster

718. Clinical Computational Models

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Topic: I.06. Computation, Modeling, and Simulation

Support: Innovative Medicines Initiative Joint Undertaking (IMI) under grant agreement no. 115300 (EU-AIMS)

Title: Identifying developmental trajectories in whole brain community structure in Autism Spectrum Disorder using multilayer community detection

Authors: ***U. BRAUN**[1], A. MOSCICKI[1], C. MOESSNANG[1], S. BARON-COHEN[2], S. DURSTON[3], A. M. PERSICO[4], W. SPOOREN[5], D. MURPHY[6], E. LOTH[6], J. BUITELAAR[7], T. BANASCHEWSKI[1], D. BRANDEIS[1,8], H. TOST[1], A. S. MEYER-LINDENBERG[1]
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Kingdom; [3]Rudolf Magnus Brain Ctr., Utrecht, Netherlands; [4]Unit of Child and Adolescent Psychiatry, Univ. of Messina, Messina, Italy; [5]Hoffmann-La Roche, Basel CH 4070, Switzerland; [6]King's Col. London, London, United Kingdom; [7]Donders Inst. for Brain, Cognition and Behaviour, Nijmegen, Netherlands; [8]Univ. of Zurich, Zurich, Switzerland

Abstract: Autism is a severe developmental disorder in which connectivity aberrations in several brain systems at different age periods have been described. Whether or not these differences are due to aberrant developmental trajectories or idiosyncratic characteristics of ASD brains remains debated. In a multicenter, longitudinal sample of 60 subjects with Autism Spectrum Disorder (ASD) and 60 healthy controls (balanced for age, sex, head motion and acquisition site), covering an age range of 7 to 27 years, we tested whether ASD subjects exhibited differential maturation of whole brain community structure. Combining functional magnetic resonance imaging data from a well-established Theory-of-Mind task and a recently described network based multilayer community detection algorithm, we detected groups of brain regions clustered together into densely interconnected structures whose interactions change during development. We compared this brain-wide community structure over development using mutual information (MI) to create maps of similar development. Additionally, we computed flexibility of the theory-of-mind brain regions which measures the number of times brain regions change their community assignment between adjacent subjects to identify periods of marked community structure reconfigurations over development. Both MI maps and flexibility differed strikingly between ASD and healthy controls. Cluster analysis revealed that healthy subjects showed 3 periods of highly similar development, while ASD subjects exhibited only 2 such periods. Interestingly, the overall similarity between the community structures over all age periods was reduced in ASD, supporting the idea of a higher systems heterogeneity in ASD. Moreover, ASD subjects showed less frequent reconfigurations of their theory-of-mind related brain areas compared to healthy subjects.
In conclusion, our results demonstrate aberrant maturation of global network architecture during a theory-of-mind task as well as altered and less frequent periods of reconfiguration of the theory-of-mind network in ASD.

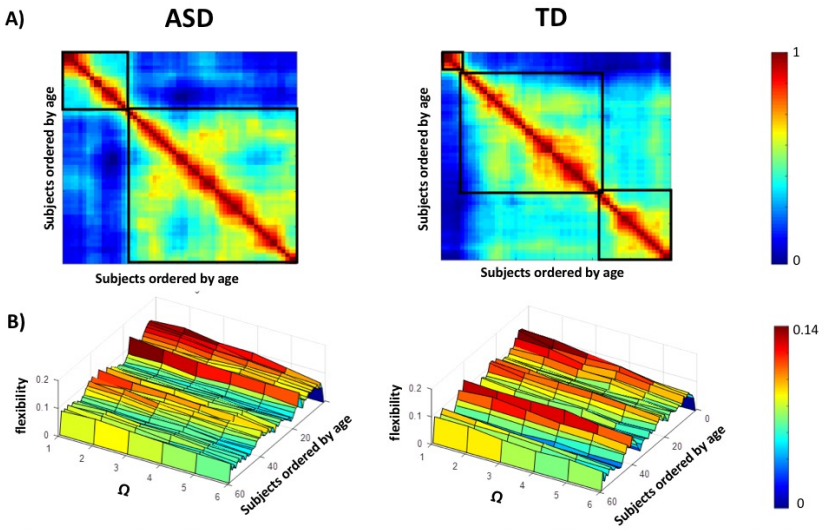

Fig1: Development of whole brain community structure in typically developing (TD) and autism spectrum disorder (ASD) subjects

A) Similarity matrix as mutual information between the community structure of ASD (left) and TD (right) subjects over development. Subjects are ordered by age, with 5 subjects per year bin. Notice the clear separation into two age/developmental clusters in ASD, while in TD the pattern falls into 3 different clusters/developmental periods.

B) Flexibility (number of community changes between ordinally ordered subjects) as a maker of system reconfigurations of the theory-of-mind system shows two major peaks in ASD and an additional pronounced peak in TD subjects in late adolescence.

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Poster

718. Clinical Computational Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 718.04/VV66

Topic: I.06. Computation, Modeling, and Simulation

Support: AG042178

AG047812

Title: Pharmacophore based screening and molecular docking probing the novel inhibitors against BACE1 of Alzheimer's disease

Authors: *P. JANGAMPALLI ADI, P. REDDY
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Abstract: The purpose of our study was to identify pharmacophore-based drugs to reduce amyloid beta (Aβ) toxicities in Alzheimer's disease (AD). Pharmacophore-based models are one of the most promising approaches in the current drug discovery process in modern biology. Aspartyl protease inhibitors, like pepstatin, are well-known potent inhibitors to reduce the cleavage of proteins. The crystal structure of the beta amyloid cleavage enzyme 1 (BACE1) protein contains 2 functional domains: ecto and internal. The ectodomain is the key functional part of catalytic cleavages is initiated by BACE1, which leads to aggregates of the pathological Aβ in AD neurons. What are the chief residues involved in the external domain catalytic process are still unknown, and currently, there are no promising BACE1 inhibitors available in the market? In the present study, we constructed a pharmacophore model of BACE1 and pepstatin, using computational screening and molecular docking. The inhibitor based pharmacophores resulted in the identification of new lead molecules showed best potentiation to reduce Aβ formation with best docking and molecular interaction studies. The top-ranking small molecules were cross checked across their suitability as drugs and toxic effects. Finalized three small molecules are potential therapeutic drug targets for the treatment of AD. Furthermore *in vitro* and *in vivo* confirmative studies are our further prospects in the development of new drugs intervention against AD.

Disclosures: P. Jangampalli Adi: None. **P. Reddy:** None.

Poster

718. Clinical Computational Models

Location: Halls A-C

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Program#/Poster#: 718.05/VV67

Topic: I.06. Computation, Modeling, and Simulation

Support: DAAD 19-02-1-0038

Title: Bioinformatics analysis of a F2 mouse dataset reveals gene networks regulating sleep homeostasis and major depressive disorder

Authors: *V. GAO[1], P. JIANG[1], J. R. SCARPA[2], K. FITZPATRICK[3], M. VITATERNA[1], A. KASARSKIS[2], F. W. TUREK[1]
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Abstract: Sleep and sleep problems are known to be linked with psychiatric disorders, though the underlying mechanisms connecting sleep and affect are not clear. To investigate these connections, we tested about 200 (C57BL/6 x 129S1/SvImJ)F2 mice in a battery of tests for affective behaviors and recorded their sleep under baseline, sleep deprived, and restraint-stressed conditions. They were genotyped at ~2,500 informative loci across the genome, and their gene-expression transcriptome was measured using microarray in the frontal cortex, hippocampus, hypothalamus, and midbrain-thalamus. Principal components analysis was used to cluster phenotypes and discover underlying relationships between them. Weighted gene coexpression network analysis and clustering were used to identify modules of coexpressed genes in each tissue. Quantitative trait loci (QTL) analysis and a causal inference test were used to identify genes whose expression levels were causal to phenotype variation.
We found that QTL for gene expression (eQTL) are largely conserved across brain regions; however, the phenotypic associations of those eQTL-regulated genes can be diverse across regions. Some coexpression modules are also conserved across brain regions, and we find that these conserved modules are mainly driven by genetic linkage. We integrated our data with publicly-available data from others' experiments to identify which of our coexpression modules are enriched for genes that are differentially expressed during sleep deprivation. By comparing the modules' association with sleep phenotypes, we hypothesize which modules act as a sleep homeostatic signal. Similarly, we also identify differentially-regulated modules in major depressive disorder (MDD). Several coexpression modules which are differentially regulated in both sleep disruption and MDD are further investigated, with a focus on two in the frontal cortex. Analysis of key drivers in the network identifies several genes, including activity-regulated

cytoskeleton-associated protein (*Arc*) as potentially playing a key role in both sleep deprivation and MDD.

Disclosures: V. Gao: None. **P. Jiang:** None. **J.R. Scarpa:** None. **K. Fitzpatrick:** None. **M. Vitaterna:** None. **A. Kasarskis:** None. **F.W. Turek:** None.

Poster

718. Clinical Computational Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 718.06/VV68

Topic: I.06. Computation, Modeling, and Simulation

Title: Bionic legs restore the dexterity, confidence and ownership in lower-limb amputees

Authors: *S. RASPOPOVIC[1], F. PETRINI[2], G. VALLE[3], P. CVANCARA[4], A. HIAIRRASSARY[5], D. GUIRAUD[5], A. ALEXANDERSSON[6], T. STIEGLITZ[7], S. MICERA[1], M. BUMBASIREVIC[8]
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Abstract: The lack of natural sensory feedback causes specific impairments to amputee patients: they do not perceive the prosthesis as a part of their body (low embodiment) and risk falls (low dexterity), hence do not rely on it and execute counterbalancing movements which increase fatigue. It also results in up to 60% of prosthesis abandonments (low confidence). Some efforts to restore sensory feedback in lower limb amputees have been conducted with non-invasive technologies, without success in solving these issues. In this work we developed the first prosthetic leg, which restores sensory feedback to amputees by means of implanted intraneural electrodes, in order to enable patients full recovery of dexterity, confidence and embodiment boosting. Two transfemoral amputees underwent the implant of 4 intraneural electrodes in the proximal section of tibial nerve for more than 100 days each. We showed that natural sensations of touch, pressure, vibration and muscle contractions could be elicited on the phantom leg, on the numerous positions over the foot sole and lower leg. Then these sensations were used within the bidirectional prosthetic control. A commercial prosthetic leg with an encoder embedded in the knee was equipped with a custom made sensorized sole, recording the pressure information from 7 positions of the foot sole. The readout of these sensors and encoder was used to drive wirelessly the stimulation of 5 active sites, eliciting natural touch under the foot sole and calf contraction, intuitively interpreted by the subject as knee flexion. The subjects then underwent a set of investigations, devoted to explore singular hypotheses: i) walking over obstacles, without

possibility to visually inspect (confidence test), ii) walking over the stairs, sand, gravel and straight lines (dexterity and mobility test) and iii) induced ownership (embodiment tests). Remarkably, the proposed intervention showed significantly increased confidence, higher dexterity and mobility, together with the clear embodiment augmentation. Natural sensory feedback from missing leg can be elicited to the transfemoral amputees, and integrated into the successful natural control and holds the promise to overcame the limitations of the present prosthetic devices.

Disclosures: **S. Raspopovic:** None. **F. Petrini:** None. **G. Valle:** None. **P. Cvancara:** None. **A. Hiairrassary:** None. **D. Guiraud:** None. **A. Alexandersson:** None. **T. Stieglitz:** None. **S. Micera:** None. **M. Bumbasirevic:** None.

Poster

718. Clinical Computational Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 718.07/VV69

Topic: I.06. Computation, Modeling, and Simulation

Support: US National Science Foundation DMS Award 1410935

Title: A mathematical network model of ischemic stroke

Authors: ***M. SARKAR**, R. A. LEE, C. J. CONTE, D. H. TERMAN
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Abstract: Brain lesions and expanding infarcts after ischemia result from multiple insults, but at its core, cell damage and death is the result of reduced oxygen and glucose supply to brain cells, which decreases mitochondrial ATP production. An immediate effect of ATP depletion is the failure of the Na^+-K^+ ATPase pump, needed to maintain proper electrochemical ion gradients. These gradients are also needed for glutamate transporters to remove glutamate from the extracellular space. The Na^+-glutamate transporters on both neurons and astrocytes can reverse their glutamate transport and secrete glutamate at concentrations capable of inducing excitotoxicity. Moreover, failure of the Na^+-K^+ ATPase pump results in elevated extracellular K^+, which leads to waves of recurrent spreading depolarizations (RSDs) in both neurons and astrocytes. We have developed a detailed biophysically-based computational model for a neuron/astrocyte network in order to explore mechanisms responsible for the initiation and propagation of recurrent cortical spreading depolarizations. The model incorporates biophysical processes not considered in the earlier models. This includes a model for the Na^+-glutamate transporter, which allows for a detailed description of reverse glutamate uptake. In particular, we consider the specific roles of elevated extracellular glutamate and K^+ in the initiation, propagation and recurrence of spreading depolarizations. Gap junctions between astrocytes are

also included in the model to understand how the strength and number of gap junction connections impact RSDs. Simulations suggest that the initiation of RSDs is due primarily to the increase in extracellular glutamate, while the propagation of RSDs is due primarily to the rise in extracellular K^+. In the model, fewer cells are required to initiate RSDs as the strength of the Na^+-K^+ pump is decreased. The evidence that gap junctions play a protective or harmful role during stroke appears mixed. At reduced gap junction strengths, a greater number of gap junctions reduced the likelihood of RSDs. However, at increased gap junction strength, more gap junctions per astrocyte increased the probability of RSDs.

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Poster

718. Clinical Computational Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 718.08/VV70

Topic: I.06. Computation, Modeling, and Simulation

Title: Modeling striatal network dynamics in disease

Authors: *A. P. PONZI[1], S. J. BARTON[2], G. V. REBEC[2], J. R. KOZLOSKI[1]
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Abstract: Dysregulated striatal information processing is thought to play a crucial role in the pathology of multiple diseases such as Huntington's disease, Parkinson's disease, depression and addiction. Previous striatal network modeling [Ponzi, A and Wickens J (2010). Sequentially switching cell assemblies in random inhibitory networks of spiking neurons in the striatum. Journal of Neuroscience, 30(17), 5894-5911. Ponzi, A and Wickens J, Optimal balance of the striatal medium spiny neuron network. PLoS Comput Biol 9, no. 4 (2013): e1002954] suggested that the normal medium spiny neuron network may be poised close to a critical state between stable and unstable dynamical regimes. To investigate how disease pathologies can affect this balance we made a similar but more detailed computational model of the striatal network comprising more biologically detailed spiny projection neurons with multiple ion channels and a network of fast spiking interneurons.
We first confirm that this more detailed model also shows a critical state in the striatally appropriate parameter regime. Next we explore how a variety of modifications, both to the individual cell ion channels and to the network structure and to synaptic properties such as excitatory drive, move the network dynamics away from this optimal critical regime. We compare these model pathological states with experimental observations from disease states, in particular from model Huntington' disease animals. This work provides insights into the physiological modifications underlying the aberrant network phenotypes and can help isolate

targets for pharmacological intervention as part of a quantitative network systems pharmacology. Finally in order to model behavioural symptom endpoints for basal ganglia diseases and therapeutics we also study how the network behaves when cortical and thalamic input varies as it might in simple discrimination behavioural tasks. As proxies for reaction times and error rates in these tasks we use the quantity of discriminative information in the striatal network. We investigate how this quantity varies with cell and network manipulations modeling disease and therapeutic states and compare results with existing experimental task studies.

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Poster

718. Clinical Computational Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 718.09/VV71

Topic: I.06. Computation, Modeling, and Simulation

Title: Towards the optimal control of nonlinear brain networks dynamics in Alzheimer's disease

Authors: L. M. SANCHEZ-RODRIGUEZ[1], Y. ITURRIA-MEDINA[3], *R. C. SOTERO[2]
[1]Biomed. Engin. Grad. Program, [2]Radiology, Univ. of Calgary, Calgary, AB, Canada; [3]Neurol. & Neurosurg., Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: We introduce the application of exogenous electric signals as an alternative for controlling the brain activity in Alzheimer's disease patients. Reports show abnormalities in the EEG spectrum as a consequence of Alzheimer's (Jeong, 2004). Fundamental research aiming to unveil the mechanisms associated with this condition is ongoing and far from offering a complete understanding of its causes and progression. Meanwhile, the application of innovative therapeutic procedures might help to reverse the effects of the disease. One criterion any proposal should fulfill is being realistic in the modeling of brain networks dynamics (Sotero et al., 2007).
We placed a set of coupled autonomous Duffing oscillators over seventy-eight regions that covered the brain's gray matter. Diffusion MRI data for healthy controls (HC) and Alzheimer's patients (AD), from the Alzheimer's Disease Neuroimaging Initiative (ADNI), was used to calculate structural connectivity matrices for the interactions between brain areas (Iturria-Medina et al., 2007-2008). Then, we proceeded to find an external signal that, inputted individually over the areas, makes the rest of them evolve towards a certain predefined state as a cost function is minimized. Previous studies have neglected the nonlinear nature of brain dynamics for the sake of mathematical simplicity. However, the choosing of Duffing oscillators for the dynamics provides both physiological reliability and easy-to-inspect effects of the non-linearities. The optimal control problem was solved by means of the so-called state-dependent Ricatti equation formalism -seldom used for biological or large-dimensional systems so far (Cimen, 2008).

Areas were ranked based on the cost of reaching absolute control. Among the areas with the lowest cost were those in the limbic system or strongly connected to it -hippocampus, amygdala, putamen, pallidum, caudate nucleus, and thalamus- for both HC and AD groups. However, regions were ranked differently in HC and AD patients. This was expected, as the progress of the pathological condition modifies the connectivity values (Iturria-Medina et al., 2016). Additionally, ranks changed with the value of the non-linearity in both HC and AD. Higher non-linearities were associated with loss of controllability from some areas. Overall, our results shed light on the nonlinear optimal control of realistic brain networks. The progress herein reported is encouraging for the development of engineering solutions to reverse the consequences of Alzheimer's disease.

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Poster

718. Clinical Computational Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 718.10/VV72

Topic: I.06. Computation, Modeling, and Simulation

Title: Shape analysis of human white matter tracts

Authors: *T. GLOZMAN[1], L. BRUCKERT[1], F. PESTILLI[2], D. W. YECIES[1], L. GUIBAS[1], K. YEOM[1]
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Abstract: Diffusion imaging coupled with tractography algorithms allows researchers to image human white matter tracts in-vivo. White matter tracts are three-dimensional structures with shapes that change over time during the course of development as well as in pathologic states. While most studies on white matter variability focus on analysis of tissue properties estimated from the diffusion data, e.g. fractional anisotropy, the shape variability of white matter tracts is much less explored. In this paper, we present a set of tools for shape analysis of white matter tracts, namely: (1) a concise geometric model of tract shapes; (2) a method for tract registration; (3) a method for deformation estimation. Our framework is useful for analysis of shape variability in white matter tracts. We demonstrate our framework by applying our methods on a dataset of 38 normally developing children of age 11 days to 8.5 years and suggest a model of canonical shape evolution on an ensemble of white matter tracts. Our framework provides a robust, quantifiable and reproducible model of changing geometric white matter shape over the course of human development that agrees with normative human head and brain growth data. Such model may improve understanding of both normal development and pathologic states and represents a novel parameter for the examination of the pediatric brain.

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Poster

718. Clinical Computational Models

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Topic: I.06. Computation, Modeling, and Simulation

Support: The Department of Anesthesia, Critical Care and Pain Medicine at MGH

Institute for Medical Engineering and Sciences

Department of Brain and Cognitive Sciences

Picower Center for Learning and Memory MIT

NIH Director's Pioneer Award

NIH Director's Transformative Research Award

Title: A computational framework for closed-loop control of general anesthesia in macaques

Authors: *S. CHAKRAVARTY[1], J. A. DONOGHUE[2], M. MAHNKE[1], D. KISHNAN[4], P. L. PURDON[4,2], E. K. MILLER[1,2], E. N. BROWN[1,2,5,3,4]
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Abstract: Post-operative cognitive dysfunction, particularly in the elderly, and anesthetic toxicity in children are major problems following general anesthesia (GA). A precise computerized titration of the anesthetic drug can potentially mitigate these problems. Here, we report a computational framework, developed based on initial experiments, to achieve precise control of the anesthetic state in a non-human primate GA model. In this framework, local field potentials are recorded from chronically implanted microelectrode arrays within prefrontal cortex as animals are anesthetized using intravenous propofol ($GABA_A$ agonist). We set a target anesthetic state. Then using this information, our proposed computerized closed-loop scheme automatically adjusts the drug infusion rate based on the subject's anesthetic state monitored via local field potential dynamics in the prefrontal cortex. This control scheme comprises two main steps, estimation and control, that are implemented in a cyclical manner. In the estimation step, the anesthetic state is estimated from special drug-system specific signatures present in the multi-tapered spectrogram of the local field potentials. From our initial experiments, we have identified

spectral features as candidate anesthetic markers to control. We use a state space model (SSM) to define the dynamics of the anesthetic drug transport to the brain and how it affects a selected marker. In this SSM, the state equations are based on a two-compartment linear pharmacokinetics setup comprising a central compartment (plasma) and an effect compartment (brain). The observation equation in this SSM, relating the amount of drug in the brain to the observed marker, is a Sigmoid-Emax model. This SSM paradigm allows us to implement a Kalman Filter strategy to estimate anesthetic state from the marker time-series. The parameters for this SSM strategy are estimated from preliminary data collected from macaques under a custom-designed infusion scheme. In the control step, we use a Linear Quadratic Regulator (LQR) to calculate the change in the drug infusion rate required to maintain the state at a given target value. The LQR framework allows us to the perform the estimation and control steps in sequence as well as determine optimal infusion rates that minimize a cost function penalizing the deviation of the anesthetic state and infusion rates from their respective desired values over the control interval. Our *in-silico* results indicate feasibility of validating this scheme in macaques and provide potential for analogous closed-loop control in patients requiring extended duration of anesthesia in the future.

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Poster

719. Cortical and Hippocampal Network Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 719.01/VV74

Topic: I.06. Computation, Modeling, and Simulation

Title: A generative model for cortical networks

Authors: *D. L. BARABASI, Z. TOROCZKAI
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Abstract: Updated experimental efforts using hemisphere-wide retrograde and anterograde tracing have provided large-scale static data about the architecture of the cortex. Previous studies of low-density interareal connectivity have found emergent scale-free and rich club properties as indicators of network heterogeneity, however these need to be revised due to the high-density nature of the cortico-cortico wiring reported in the recent experimental studies. To understand the level of specificity and connection heterogeneity of the cortical network one needs to take an

alternative approach that is more suitable for dense, directed, spatial networks. Past work has introduced a simple core-periphery detection method based on clique distribution analysis, showing a strong core-periphery organization of the cortex in both macaques and mice when compared to appropriately chosen null-models, which was further validated using stochastic block modeling analysis. Physically, tracing experiments have revealed in both macaque and mouse brains the action of the so-called Exponential Distance Rule (EDR): an exponential decay of connection probability with distance. A prior network model based on the EDR was defined at the level of functional areas and captured many features of the experimentally obtained network, however, as we show here it fails in other measures, such as in identifying the core-periphery structure, found in experiments. Here we introduce a neuronal-level network model based on the EDR, which, given a a parcellation of the cortex into functional areas, naturally generates the interareal network. This new model now also quantitatively captures the features missed by the areal-level model and shows that the core-periphery structure emerges due both to the EDR and the distribution of area sizes and their relative positioning. These findings demonstrate that the cortical network cannot be modeled as a simple connectivity graph at the areal level, but one needs multiscale network models that are intricately tied with the functional parcellation of the cortex and the morphological properties of the cortical plate.

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Poster

719. Cortical and Hippocampal Network Models

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Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R01EB022889-01

Title: Human neocortical neurosolver (HNN): A new computational tool for localizing and interpreting human neocortical dynamics

Authors: *S. A. NEYMOTIN[1], N. PELED[2], R. A. MCDOUGAL[3], N. T. CARNEVALE[3], M. L. HINES[3], M. HAMALAINEN[4], S. R. JONES[1,5]
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Abstract: MEG/EEG are the leading methods to non-invasively record human neural dynamics with millisecond temporal resolution. However, it is extremely difficult to infer the underlying cellular and circuit level origins of these "macro-scale" signals without simultaneous invasive

recordings. This limits the translation of MEG/EEG or ECoG findings into novel principles of information processing, or into new treatment modalities for neural pathologies. As such, there is a pressing need, and a unique opportunity, to relate the "macro-scale" signals to their underlying "meso-scale" generators.
To address this need, we are building the Human Neocortical Neurosolver (HNN), an open-source neural modeling tool designed to help researchers/clinicians interpret human imaging data. HNN presents a convenient GUI to an anatomically and biophysically detailed model of human thalamocortical brain circuits, which makes it easier to generate and evaluate hypotheses of the mechanistic origin of signals measured with MEG/EEG or intracranial ECoG. A unique feature of HNN's model is that it accounts for the biophysics generating the primary electric currents underlying such data, so simulation results are directly comparable to source localized data (nano-Ampere-meters); this enables precise tuning of model parameters to match characteristics of recorded signals.
We are integrating the circuit-level modeling with the minimum-norm-estimate (MNE) source localization software, so researchers can compute MEG/EEG source estimates and test hypotheses on the circuit origin of their data in one software package. Our goal is to design HNN to be useful to researchers with no formal computational neural modeling or coding experience. Visualization plugins, which provide 3D views of model cells and their connectivity, will aid intuition on how circuit architecture can influence neocortical dynamics. We are also building resources for freely using and expanding the software through the Neuroscience Gateway Portal, and online documentation and a user forum for interaction between users and developers. We will present the initial construction of our tool and describe its use in studying the circuit-level origin of some of the most commonly measured MEG/EEG and ECoG signal: event related potentials (ERPs) and low frequency rhythms (alpha/beta/gamma).

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Poster

719. Cortical and Hippocampal Network Models

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Title: A cortical microcircuit model with heterogeneous excitatory and inhibitory neurons

Authors: *N. L. KAMIJI, R. SHIMOURA, R. F. PENA, V. L. CORDEIRO, C. ROMARO, C. C. CEBALLOS, A. C. ROQUE
Deptarment of Physics, FFCLRP, Univ. of Sao Paulo, Ribeirao Preto, Brazil

Abstract: Large-scale cortical network models often assume that the dynamic state of the network is controlled by the balance between excitatory and inhibitory synaptic inputs. Most cortical models that rely on excitation-inhibition (EI) balance have been studied in the context of random networks of leaky integrate-and-fire (LIF) neurons but recently the EI balance condition has been successfully extended by Potjans and Diesmann to a multilayered model of cortical microcircuitry. The Potjans-Diesmann (PD) model integrates experimental data from many different sources into a four-layer model with two cell types, excitatory and inhibitory, connected according to realistic layer and cell-type specific connectivity. The excitatory and inhibitory neurons of the PD model are described by the same LIF model, and a question that poses itself is whether the properties of the PD model under EI balance condition remain valid when the excitatory and inhibitory neurons become different. Here we answer this question by replacing the excitatory and inhibitory LIF neurons of the original PD model by Izhikevich regular-spiking (RS) and fast-spiking (FS) neurons, respectively, generating a heterogeneous version of the PD (hPD) model. We adjusted the synaptic parameters of the hPD model to turn it into a balanced model and studied the firing patterns of the eight cell populations under different conditions: without external input (spontaneous activity) and when the network was submitted to random input spikes applied to layers 4 and 6 to mimic thalamic inputs, as done by Potjans and Diesmann in their original work. In all cases the balanced hPD model showed similar behavior to the one presented by the original balanced PD model. In conclusion, the heterogeneous version of the Potjans-Diesmann model can be an upgrade of the original Potjans-Diesmann model to a more realistic model of the cortical microcircuit.

Disclosures: **N.L. Kamiji:** None. **R. Shimoura:** None. **R.F. Pena:** None. **V.L. Cordeiro:** None. **C. Romaro:** None. **C.C. Ceballos:** None. **A.C. Roque:** None.

Poster

719. Cortical and Hippocampal Network Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 719.04/VV77

Topic: I.06. Computation, Modeling, and Simulation

Support: FAPESP Grant 2015/50122-0

DFG-GRTK Grant 1740/2

FAPESP CEPID NeuroMat Grant 2013/07699-0

FAPESP Grant 2013/25667-8

CNPq Research Productivity Grant 306251/2014-0

Title: Noise-enhanced transition from synchronized to desynchronized states in a cortical network model

Authors: *R. D. PENA[1], M. ZAKS[2], A. C. R[1]
[1]Univ. of São Paulo, Ribeirão Preto, Brazil; [2]Humboldt Univ. of Berlin, Berlin, Germany

Abstract: Neuronal activity recorded in the cerebral cortex displays complex dynamic patterns. These patterns form a continuum of states ranging from a synchronized state, characterized by low-frequency oscillation in the population firing rate and up/down switching in the single-neuron membrane potential, to a desynchronized state, characterized by a roughly constant population firing rate and irregular single-neuron firing. Being related to the instantaneous state of the brain, these regimes are separated by repeated transitions. The synchronized state is more prominent during slow-wave sleep and anesthesia while the desynchronized state is more prominent during states of wakefulness and REM sleep. The mechanisms responsible for synchronized-desynchronized transitions are not completely known and here we study the effect of synaptic noise on these transitions. We use our recently proposed random network model with mixed neuronal types (Front Comput Neurosci 8:103, 2014), which displays spontaneous network oscillations that resemble the alternation of up and down states observed in the synchronized cortical state. The model is described by deterministic equations and we add synaptic noise to it modeled by an Ornstein-Uhlenbeck process. The effect of noise was to make the network state change stochastically between synchronized and desynchronized states. Systematic analysis of firing rates, power spectra and voltage series confirms that the characteristics of the two basic states are very similar to those of desynchronized and synchronized cortical states: in the desynchronized state neurons have very low collective firing rate and are weakly correlated; in the synchronized state neurons have a collective oscillatory activity where their membrane voltages fluctuate between a hyperpolarized (down) state and a depolarized (up) state. By varying the noise intensity and using the mean duration at each state as a prevalence criterion, we observe that noise facilitates transitions from the desynchronized to the synchronized state and hinders the reverse transitions. Our results suggest that synaptic noise may be an important mechanism underlying transitions between desynchronized and synchronized states in cortical networks.

Disclosures: **R.D. Pena:** None. **M. Zaks:** None. **A.C. R:** None.

Poster

719. Cortical and Hippocampal Network Models

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Support: NIH P41 GM103545-18

BMBF (German Ministry of Education and Research) grant 01GQ1510 OptiStim

NSF IIS CRCNS #1515168

DFG (German Research Foundation) EXC1086 BrainLinks-BrainTools

NSF EEC-1028725

Title: Combining computational neuroscience and electrophysiology for optimal cortical electric stimulation

Authors: *M. DANNHAUER[1], K. SHAYESTEHFARD[2], S. GULER[2], D. J. CALDWELL[3], J. A. CRONIN[3], A. GKOGKIDIS[5], R. MACLEOD[1], T. BALL[5], J. G. OJEMANN[4], D. BROOKS[2]
[1]Scientific Computing and Imaging Inst., Univ. of Utah, Salt Lake City, UT; [2]Electrical and Computer Engin., Northeastern Univ., Boston, MA; [3]Dept. of Bioengineering, [4]Dept Neurosurg., Univ. of Washington, Seattle, WA; [5]Universtity Med. Ctr. Freiburg, Freiburg, Germany

Abstract: Electrodes arrays placed subdurally on the cortical surface (electrocorticography, ECoG, using strip and grid arrays) or deeper in brain tissue (depth electrodes and stereotactic needles) are frequently deployed to study intrinsic brain activity with high spatio-temporal resolution (e.g., in epileptic patients). They are also increasingly used to inject current to modulate brain activity. Consenting subjects undergo current stimulation on different scales (e.g., standard ECoG and micro-electrocorticography, μECoG), using varying current levels and patterns to elucidate or rehabilitate brain function. However, little is known about either the optimal design or use of these systems. The project reported on in this abstract has clinical, computational, and experimental components across three sites in the US and one in Germany, collaborating synergistically to study these questions. In our clinical work, at University of Washington, we monitor current spread with high spatial and temporal fidelity to better understand tissue properties, current delivery and its effect on brain functioning, as well as to validate our computational models. Validated computational models and efficient tailored optimization methods, developed at University of Utah and Northeastern University, allow us to to optimize current in target regions-of-interest (ROIs) while constraining it in non-ROI regions for safety as well as enhanced targeting. In the German component, at University of Freiburg) we apply these models to validate and design cortical and subcortical indwelling μECoG arrays in

phantoms (Fig. 2), animals (ovine), and humans using computed patterns of low-amplitude currents delivered to specific brain ROIs. We also deploy a sensitive infrared camera to monitor induced temperature distribution. In the future we will use both in vivo ECoG and μECoG measurements of stimulation-evoked brain responses to design and assess the functional effects of current patterns and thus improve both designs and deployment of cortical arrays.

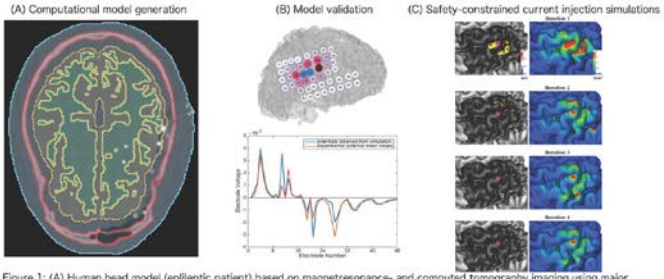

Figure 1: (A) Human head model (epileptic patient) based on magnetresonance- and computed tomography imaging using major resistive tissues; (B) Validation of modeling (Finite element method) accuracy using measured potentials arising from experimental current injection; (C) Simulations of optimal current injection for gyral target area (purple) using safety constraints avoiding 'hot-spots' (yellow = local current density peaks) in critical region (black, color refer to left column) below ECoG grid.

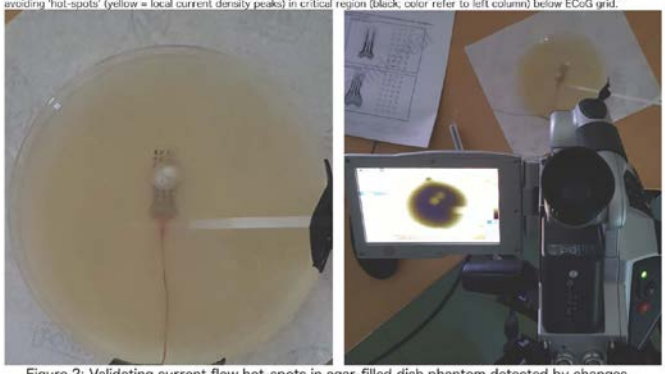

Figure 2: Validating current flow hot-spots in agar-filled dish phantom detected by changes of local heat distribution (recorded by a thermal camera)

Disclosures: M. Dannhauer: None. **K. Shayestehfard:** None. **S. Guler:** None. **D.J. Caldwell:** None. **J.A. Cronin:** None. **A. Gkogkidis:** None. **R. MacLeod:** None. **T. Ball:** None. **J.G. Ojemann:** None. **D. Brooks:** None.

Poster

719. Cortical and Hippocampal Network Models

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Program#/Poster#: 719.06/VV79

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Support: 5R21HD083956-02

1R01EB017337-01

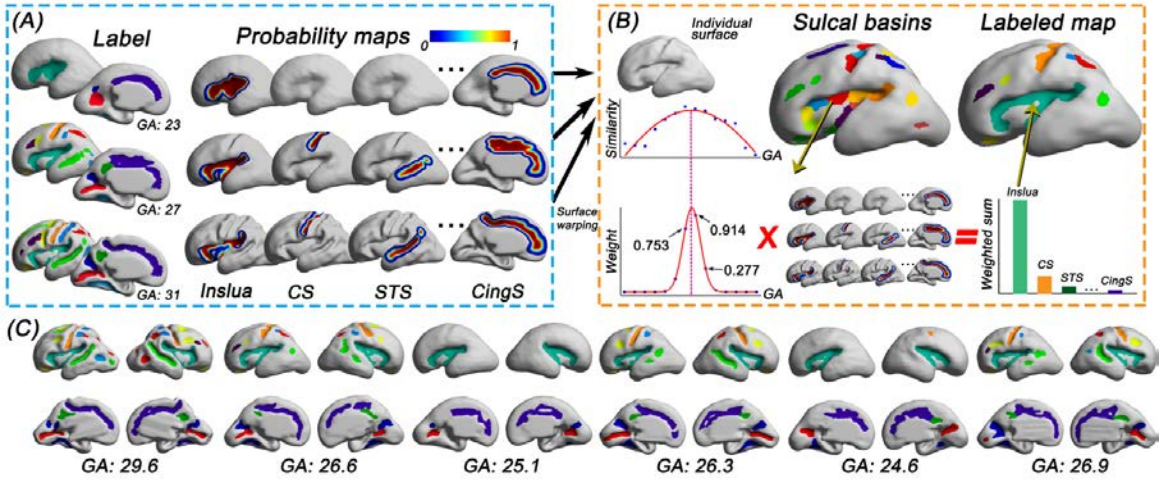
1U01HD087211-01

U10HL068270

Title: Automatic labeling of cortical sulci in human fetal brains

Authors: *H. YUN[1], B. GAGOSKI[1], C. ROLLINS[2], C. ORTINAU[4], E. YANG[3], P. E. GRANT[1], K. IM[1]
[1]Newborn Med., [2]Dept. of Neurol., [3]Dept. of Radiology, Boston Children's Hosp., Boston, MA; [4]Dept. of Pediatrics, Washington Univ. Sch. of Med., St. Louis, MO

Abstract: In the human cerebral cortex, primary sulci are important anatomical landmarks for inferring cortical functional organization and their overall spatial patterns are relatively invariant across individuals[1,2]. Using spatial patterns and geometric features of the sulci, several studies have implemented automated methods for labeling sulci to analyze cortical folding pattern[3-5]. However, labeling sulci in fetal brain is still challenging, because the sulcal pattern undergoes dramatic changes during fetal stage. The aim of this study is to automatically label early primary sulci for individual fetuses based on the temporal dynamics of sulcal pattern.For labeling with temporal dynamics, we combined sulcal patterns of 9 fetal brain atlases from 23 to 31 gestational age (GA), which is crucial period for gyrification[6,7]. Sulcal regions on the templates were defined using cortical curvature maps on cortical plate surfaces, and then manually assigned to 20 anatomical labels including a non-sulcal and 19 sulcal regions. Spatial probability maps of the labels were generated by smoothing each label on the surface templates and used as prior information for individual sulcal labeling (Fig 1A). Then, the prior information was aligned to individual surfaces by 2D sphere warping[8]. To consider the temporal change of the brain, we set weights for the aligned prior information. The weight of each template was estimated by a curve, fitted on similarities of folding patterns between the individual and templates (Fig 1B). Finally, we averaged the weighed information within a sulcal region on an individual surface, and assigned one of the 20 labels with the highest average. To validate our procedure, sulcal labels were automatically assigned to 6 individual fetal brains (GA range: 24.6 - 29.6) and the results were compared with visual assessment. The labeling results were concurrent with manual assignment (Fig 1C), showing high accuracy of the automatic labeling. Our method may provide a useful tool for automatic regional analysis of the fetal brain at the primary sulcal level.



Disclosures: **H. Yun:** None. **B. Gagoski:** None. **C. Rollins:** None. **C. Ortinau:** None. **E. Yang:** None. **P.E. Grant:** None. **K. Im:** None.

Poster

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Topic: I.06. Computation, Modeling, and Simulation

Support: UC MRPI (MR-15-328909)

ONR (MURI: N000141310672)

Title: Selective activation of cortical neurons by extracellular electrical stimulation

Authors: *M. KOMAROV, P. MALERBA, E. HALGREN, M. BAZHENOV
Univ. of California San Diego, LA Jolla, CA

Abstract: Brain stimulation is widely used for a number of reasons: to probe the neural system to learn about its properties, to normalize dysfunction (e.g., deep brain stimulation for Parkinsonian patients, tDCS for stroke patients), or as a method to manipulate brain activity. While the practice is widespread and scalable we still chose stimulus parameters through trial and error because of the difficulty in predicting the specific effects of electrical stimulation on brain tissue. In particular, it is not known which category of cells (if any) are going to spike due to an input, and which specific synaptic mechanisms are going to be recruited and modulated by a given stimulation protocol. Furthermore, depending on the goal of stimulation, the relevant effect could be driving cells to spike versus inducing sub-threshold changes. Empirically, stimulation can synchronize, de-synchronize, excite and/or suppress neuronal activity. But predicting these effects from biophysics and cortical anatomy has not been possible.
In this work, we develop a method that estimates the effect of the extracellular electrical stimulation on different types of cortical neurons. Our approach is based on calculation of the activation function [1], induced by the current density in the tissue under the stimulation electrode. The activation function represents the effective current across neuronal membranes. We convolve this activation with the statistical distribution of the axonal and dendritic arborizations of different cell types obtained from public databases of morphological reconstructions of cortical neurons. Combined with myelination properties, this is used to predict thedirect activation probabilities of different cortical cell types. These probabilities are then fed through a computational neural model of the cortex with realistic channel and synaptic elements, to predict the indirect effects of stimulation. Here we report the phasic effects of relatively strong and short (~200) stimulation pulses, as well as changes in baseline activity induced by weak and long stimulation. Our work predicts the selectivity of intracranial cortical stimulation across cell

types and layers, the focal activation of layer I axons due to cortical surface stimulation, and the optimal stimulation intensity capable to elicit cell activation lasting beyond the end of stimulation.
Rattay F. Ways to approximate current-distance relations for electrically stimulated fibers. J Theor Biol. 1987;125(3):339-49.

Disclosures: **M. Komarov:** None. **P. Malerba:** None. **E. Halgren:** None. **M. Bazhenov:** None.

Poster

719. Cortical and Hippocampal Network Models

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FAPESP Postdoctorate Grant 016/03855-5

FAPESP Doctorate Grant 2013/25667-8

CNPq Research Productivity Grant 306251/2014-0

Title: A stochastic cortical microcircuit model

Authors: ***A. C. ROQUE**, N. L. KAMIJI, V. L. CORDEIRO, C. C. CEBALLOS, R. O. SHIMOURA, R. F. O. PENA, C. ROMARO
Univ. de Sao Paulo, Ribeirao Preto, Brazil

Abstract: Cortical neurons in vivo display irregular firing patterns and this stochasticity may have important consequences for network behavior. So, it is important to have stochastic network models to study the effect of noise on their dynamic activity patterns. There are basically two types of noise model for a neuron: spike generation is modeled deterministically and noise enters the dynamics via additional stochastic terms, or spike generation is directly modeled as a stochastic process. Recently, Galves and Loecherbach (J. Stat. Phys. 151, 896-921, 2013) introduced a neural model of the latter type in which the firing of a neuron at a given time is a random event with probability given by a monotonically increasing function of its membrane potential. The model of Galves and Loecherbach (GL) has as one of its components a graph of interactions between neurons. Here it is assumed that this graph has the structure of the Potjans and Diesmann (PD) cortical microcircuit model (Cereb. Cortex 24, 785-806, 2014). The PD model has four layers and two neuron types, excitatory and inhibitory, so that there are eight cell populations. The PD model replicates well the experimental distribution of spike rates across these cell populations. In this work, the leaky integrate-and-fire neurons of the original PD model

were replaced by stochastic GL neuron models, thus generating a stochastic version of the PD (sPD) model. The firing patterns of the eight cell populations of the sPD model were studied and characterized in the two-dimensional diagram spanned by the excitatory and inhibitory synaptic weights under different conditions: without external input (self-sustained activity) and when the network is submitted to random input spikes applied to layers 4 and 6 to simulate thalamic inputs, as done by Potjans and Diesmann in their original work. The average spiking behavior per cell population of the sPD model is similar to the one of the deterministic PD model, indicating that the stochastic version of the PD model is consistent with known experimental results. Therefore, the sPD model can be a useful replacement for the original PD model in studies that require comparison between stochastic and deterministic models.

Disclosures: A.C. Roque: None. **N.L. Kamiji:** None. **V.L. Cordeiro:** None. **C.C. Ceballos:** None. **R.O. Shimoura:** None. **R.F.O. Pena:** None. **C. Romaro:** None.

Poster

719. Cortical and Hippocampal Network Models

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Program#/Poster#: 719.09/VV82

Topic: I.06. Computation, Modeling, and Simulation

Support: National Science Foundation Award IIS-1302125,

Intel Corporation

Northrop Grumman Aerospace Systems

Title: Sparse coding and dimensionality reduction in cortex

Authors: *E. ROUNDS[1], M. BEYELER[3], K. D. CARLSON[4], J. L. KRICHMAR[1], N. DUTT[2]
[1]Cognitive Sci., [2]Computer Sci., Univ. of California, Irvine, Irvine, CA; [3]Psychology, Univ. of Washington, Seattle, WA; [4]Sandia Natl. Labs., Albuquerque, NM

Abstract: Supported by recent computational studies, nonnegative sparse coding (NSC) is emerging as a ubiquitous coding strategy across brain regions and modalities. A combination of nonnegative matrix factorization (NMF) and sparse coding, NSC allows populations of neurons to collectively encode high-dimensional stimuli spaces using a compressed, sparse, and parts-based neuronal code. Specifically, we argue that neuronal circuits can 1) achieve sparse codes through competition, and 2) implement NMF by utilizing spike-timing dependent plasticity with homeostasis (STDPH). We applied NMF to two different datasets: 1) receptive fields in the dorsal subregion of the medial superior temporal area (MSTd), and 2) neurophysiological and behavioral recordings from rat retrosplenial cortex (RSC). In both cases, we were able to show that applying NMF to major inputs into these brain regions can result in a sparse representation

that captures important aspects of neuronal response properties of these brain regions. Furthermore, we found similar results applying STDPH to the RSC dataset. These findings support a growing body of evidence that suggests biological neurons use plasticity, such as STDPH, to produce sparse, compact stimulus representations that vastly reduce the dimensionality of their inputs.

Disclosures: E. Rounds: None. **M. Beyeler:** None. **K.D. Carlson:** None. **J.L. Krichmar:** None. **N. Dutt:** None.

Poster

719. Cortical and Hippocampal Network Models

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Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1U01GM104604

NIH Grant EB001978

ONR Grant N00014-13-1-0211

Title: Anatomic determinants of spatiotemporal patterns of activity in a NEURON-Admittance Method study of hippocampal protheses

Authors: *C. S. BINGHAM[1], K. LOIZOS[3], G. J. YU[2], J.-M. C. BOUTEILLER[1], D. SONG[5], G. LAZZI[4], T. W. BERGER[1]
[1]Biomed. Engin., [2]USC, Los Angeles, CA; [4]Electrical and Computer Engin., [3]Univ. of Utah, Salt Lake City, UT; [5]Biomed. Engin., Univ. of Southern California Dept. of Biomed. Engin., Los Angeles, CA

Abstract: The ideal form of a neural-interfacing device is highly dependent upon the anatomy of the region with which it is meant to interface. Multiple-electrode Arrays provide a system which can be adapted to various neural geometries. Computational models of stimulating systems have proven useful for evaluating electrode placement and stimulation protocols, but have yet to be adequately adapted to the unique features of the hippocampus. As an approach to understanding potential memory restorative devices, a NEURON-Admittance Method model was constructed to predict the direct and synaptic response of a region of the rat dentate gyrus to electrical stimulation of the perforant path. The model comprises detailed compartmental models of 50,000 granule cells and 10,000 entorhinal cortical axons in a computer reconstruction of a 400 μm coronal slice of hippocampal tissue. A validation of estimated local field potentials against experimental recordings is presented. Further, a parametric analysis of the impact of neuronal morphometry and branching complexity on patterns of activity was performed. Beyond

deepening understanding of the hippocampal tissue system, establishment of this model provides a method to evaluate candidate stimulating devices and protocols.
1

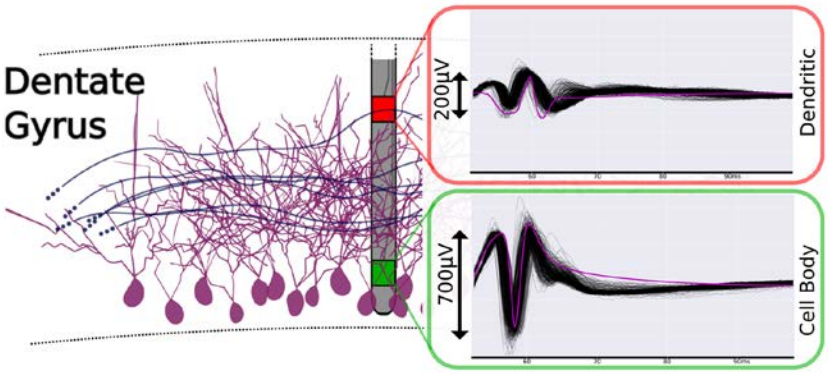

Figure. Predicted LFPs (magenta signals) capture characteristic dipole and time-course of experimental recordings (black signals).

Disclosures: C.S. Bingham: None. **K. Loizos:** None. **G.J. Yu:** None. **J.C. Bouteiller:** None. **D. Song:** None. **G. Lazzi:** None. **T.W. Berger:** None.

Poster

719. Cortical and Hippocampal Network Models

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Program#/Poster#: 719.11/VV84

Topic: I.06. Computation, Modeling, and Simulation

Support: NSERC Discovery

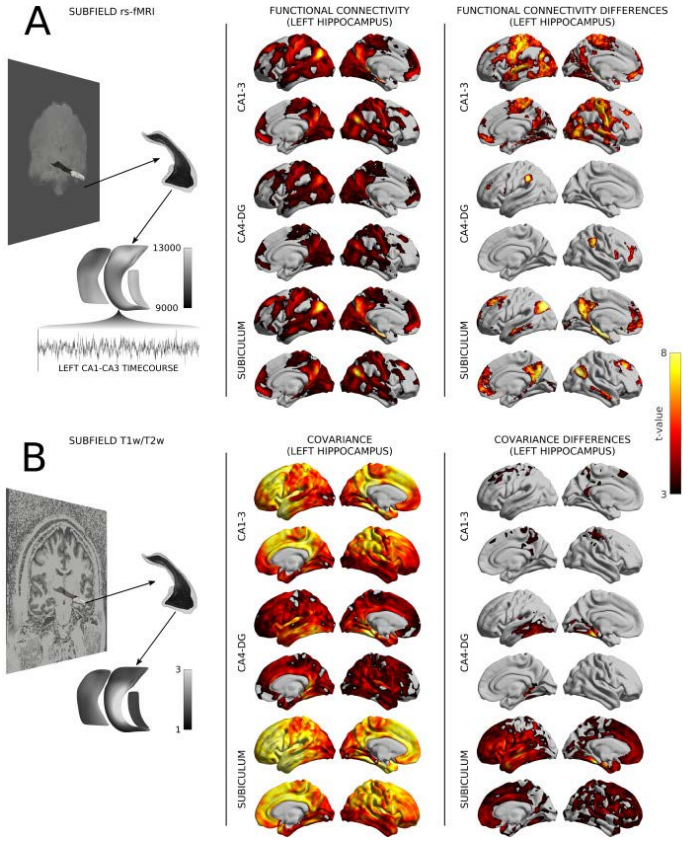
CIHR/SickKids

Title: Multimodal characterization of the mesial temporal lobe

Authors: *R. VOS DE WAEL[1], B. CALDAIROU[1], B. JEFFERIES[2], J. SMALLWOOD[2], N. BERNASCONI[1], B. C. BERNHARDT[1]
[1]McConnell Brain Imaging, McGill Univ., Montreal, QC, Canada; [2]Dept. of Psychology, Univ. of York, York, United Kingdom

Abstract: Background. The hippocampus consists of subfields with distinct anatomic properties, thought to play different functional roles. Recent advances in magnetic resonance imaging have provided guidelines to segment subfields in-vivo, and to study their internal organization and connectivity to other regions of cortex. We provide an overview of subfield-specific networks

based on resting-state functional connectivity and covariance mapping of T1w/T2w intensity, a proxy for cortical myelin.
Methods. In 100 healthy individuals (29±4 yrs, 43 men) from the human connectome project dataset, we segmented hippocampal subfields (CA1-3, CA4-DG) and the subiculum using a surface-based algorithm. We generated surfaces running through the core of each subfield, on which we sampled resting-state fMRI signals from four 15-min scans. These signals were correlated with those of the cortical surface. We also mapped subfield-specific networks using T1w/T2w covariance analysis. We studied inter-subfield differences in connectivity using fixed-effects models and covariance differences using linear interactions.
Results. All left subfields showed bilateral functional connections to core default mode nodes, i.e., angular, medial parietal, and medial frontal cortices (Fig. A).



Functional connectivity was weakest when seeding from CA4-DG. Covariance patterns showed only modest similarity to functional networks (surface-wide correlations r=.16-.26 across subfields), highlighting mainly fronto-limbic targets (prefrontal and anterior temporal cortices; Fig. B). While subiculum covariance was higher than that of other subfields in most cortex, CA4-DG covariance showed higher covariance with fusiform areas (Fig. B).
Conclusions. Our approach provides new insights on the embedding of subfields into functional and structural networks. T1w/T2w covariance analysis may identify networks with microstructural properties resembling those of individual hippocampal subfields, but these networks may not necessarily maintain significant functional links with the subfields.

Disclosures: **R. Vos De Wael:** None. **B. Caldairou:** None. **B. Jefferies:** None. **J. Smallwood:** None. **N. Bernasconi:** None. **B.C. Bernhardt:** None.

Poster

719. Cortical and Hippocampal Network Models

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Topic: I.06. Computation, Modeling, and Simulation

Support: NSF grant IIS-1526642

AFOSR grant FA9550-15-1-0398

Title: Structural and dynamic properties of critical associative memory networks

Authors: *D. ZHANG[1], C. ZHANG[1], A. B. STEPANYANTS[2]
[1]Dept. of Physics, [2]Physics, Northeastern Univ., Boston, MA

Abstract: The ability of neural networks to associate successive states of network activity lies at the basis of various cognitive functions. In this study, we hypothesize that ubiquitous features of cortical network structure and dynamics develop as a result of continual memory storage. To test this hypothesis, we consider recurrent McCulloch and Pitts networks in which neurons may belong to different classes defined by their excitatory or inhibitory nature, firing probability, and robustness to noise. Learning in the network is mediated by changes in connection weights in the presence of constraints on the l1-norms of presynaptic weights of individual neurons. To determine the memory storage capacity of the network we train the network on a set of random sequences of different lengths and subsequently test the retrieval of learned memories. To retrieve a learned sequence, we initialize the network state at the beginning of the sequence and monitor memory playout. The sequence is considered to be retrieved successfully if the network states during the retrieval do not deviate substantially from the learned sequence. The maximum (critical) capacity of the network is defined as the sequence length for which the success rate in memory retrieval equals 0.5. We performed numerical simulations for networks of 400 neurons and also solved the problem theoretically in the limit of large networks by using the replica theory. The results show that critical networks have unique structural and dynamical properties which resemble those observed in many cortical systems. First, we find that, consistent with the experimental data, probability of inhibitory connections in critical networks is greater than 0.5, whereas excitatory connectivity is sparse with connection probabilities less than 0.5. Second, we find that with increasing robustness, critical networks exhibit a phase transition from networks with ordered dynamics quickly terminating in a frozen state, to networks with chaotic dynamics during which neurons exhibit irregular and correlated firing activity with average correlation coefficients in the 0.1-0.2 range. Finally, we show that the observed transition is accompanied

with the emergence of neuron clusters, existence of which is suggested by recent experimental studies. These results are consistent with the idea that cortical networks are operating in a critical state configured at the edge of order-to-chaos phase transition.

Disclosures: D. Zhang: None. **C. Zhang:** None. **A.B. Stepanyants:** None.

Poster

719. Cortical and Hippocampal Network Models

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Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 719.13/VV86

Topic: I.06. Computation, Modeling, and Simulation

Support: AFOSR Grant FA9550-15-1-0398

NSF Grant IIS-1526642

Title: Robustness to fluctuations in neural activity is reflected in the structure of critical associative memory networks

Authors: *C. ZHANG[1], D. ZHANG[2], A. B. STEPANYANTS[1]
[1]Physics, [2]Northeastern Univ., Boston, MA

Abstract: Neural networks in the brain have the ability to function reliably despite various sources of noise in synaptic transmission. In this study, we consider associative memory storage in the presence of fluctuations in generation/propagation of action potentials and spontaneous firing. We examine how the robustness in memory recall affects the memory storage capacity and structural properties of the network. Specifically, we train recurrent networks of excitatory and inhibitory McCulloch and Pitts neurons to store predefined temporal sequences of network states. Learning is carried out in the presence of sign constraints on the weights of postsynaptic connections of each neuron and homeostatic constraints on the weights of presynaptic inputs. Errors in the inputs, j, to a given neuron are described by probabilities, p_j, while errors in the neuron's output are characterized by the probability p_{out}. Each neuron in the model is required to associate noisy input patterns with correct outputs with the probability of 1-p_{out}. The latter characterizes the robustness of the network to firing fluctuations. The probability of successful learning decreases with sequence length, and at the probability of 0.5 the network is said to be at critical capacity. We use the replica theory from statistical physics [1-3], as well as numerical simulations to determine the memory storage capacity of such robust, critical networks and examine their structural properties as a function of model parameters. We compare the results of the model to known features of cortical connectivity.
[1] Brunel, N., Hakim, V., Isope, P., Nadal, J.P., and Barbour, B., Optimal information storage and the distribution of synaptic weights: perceptron versus Purkinje cell, Neuron, 43, 745-757,

2004.
[2] Chapeton, J., Fares, T., LaSota, D., and Stepanyants, A., Efficient associative memory storage in cortical circuits of inhibitory and excitatory neurons, PNAS, 109(51): E3614-E3622, 2012.
[3] Chapeton, J., Gala, R., and Stepanyants, A., Effects of homeostatic constraints on associative memory storage and synaptic connectivity of cortical circuits, Frontiers in Computational Neuroscience 9:74, 2015.

Disclosures: C. Zhang: None. **D. Zhang:** None. **A.B. Stepanyants:** None.

Poster

719. Cortical and Hippocampal Network Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 719.14/VV87

Topic: I.06. Computation, Modeling, and Simulation

Support: Spanish MinEco grant BES-2013-065100

Spanish MinEco project BFU2012-33413

Spanish MinEco project MTM2015-71509-C2-1-R

Title: Basins of attraction in neural networks: A computational study

Authors: *B. ROVIRA, A. ROXIN
Ctr. De Recerca Matemàtica, Bellaterra, Spain

Abstract: The study of memory storage and retrieval with models of attractor neural networks dates back to the 1980's [5]. In such models memory is defined as a persistent state of the dynamics of the network, which is stored in the synaptic weight matrix [4]. Introduction of tools inherited from statistical physics, in particular the spin glass theory created for the study of magnets, allowed analytical study of the models [1]. In particular the capacity, defined as the maximum number of fixed points that the network is able to store, is still one of the main questions in the field [2, 7]. However, little is known about the basins of attraction of these fixed points.
We present a computational study of the basins of attraction in a network of sparse binary synapses with continuous on-line learning, similar to the Amit-Fusi model [3] but with an asymmetric learning rule, which is beneficial for performance. We study the connectivity of the network once the steady state is reached, and compare its properties with experimental data. We study the stability of the attractors under an homogeneous external input, which we use as a bifurcation parameter. To measure the basin of attraction, we test initial conditions increasingly perturbed from the attractor, measuring the hamming distance between initial condition and

intended attractor. We also study the stability of the fixed points under increasing synaptic noise, and the ability of the system to visit different attractors when drived by noise. Finally, synaptic depression dynamics are introduced to recreate hippocampal replay situations [6].
We find that the asymmetric rule increases the resilience of the model against different depression probabilities, and that the resulting connectivity has, when parameters are in their optimal values, similar properties to rat's cortical tissue. Basins of attraction can be tuned using both external input and depression probability, and the use of synaptic depression allows the system to visit stable attractors that would otherwise remain hidden.
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(7) S. Romani et al., Neural Computation, June 2013, 1-22.

Disclosures: **B. Rovira:** None. **A. Roxin:** None.

Poster

719. Cortical and Hippocampal Network Models

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 719.15/VV88

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R01 EB022862

NSF DMS-1516881

Title: Predicting emergent sequences from network connectivity

Authors: K. MORRISON[1], C. PARMELEE[2], S. MOORE[1], *C. P. CURTO[3]
[1]Mathematics, Univ. of Northern Colorado, Greeley, CO; [2]Mathematics, Keene State, Keene, NH; [3]Mathematics, The Pennsylvania State Univ., University Park, PA

Abstract: Many networks in the brain exhibit *internally generated* patterns of activity -- that is, patterns of neuronal firing that are shaped by intrinsic properties of the network rather than by an external input. Such dynamics are believed to underlie many brain functions, ranging from central pattern generators for locomotion to emergent sequences in cortex and hippocampus. To

isolate the role of network connectivity in shaping emergent dynamics, we previously introduced the *Combinatorial Threshold Linear Network* (CTLN) model. This model has binary synapses, simple perceptron-like neurons, and uniform external input, ensuring that the emergent dynamics are controlled solely by the structure of connectivity, dictated by an underlying directed graph G. The CTLN model naturally gives rise to sequential neuronal activity, even when G is densely-connected and has no obvious chain-like architecture. This allows us to study how network connectivity shapes emergent sequences. We found that the degree profile (the set of in/out-degrees) of a graph is a surprisingly poor indicator of network dynamics; networks with matching degree profiles can have dramatically different dynamics -- including different numbers of attractors, different types of attractors (fixed point, limit cycle, or chaotic), and different sequences.
In this work, we present a sequence prediction algorithm to predict emergent sequences from a purely graph-theoretic analysis of G. The algorithm removes nodes in order to decompose graphs down to a core cycle, and then reconstructs them to arrive at a final sequence. It is tailored to oriented graphs with no sinks, as we have proven that associated CTLNs will have no stable fixed points, and it predicts both the number of dynamic attractors and the sequence of neuronal firing. The algorithm accurately predicts all emergent sequences for 142 of the 160 permutation-inequivalent oriented graphs with no sinks on n <= 5 neurons. Furthermore, we developed a new system of labeling graphs based on the decomposition rules. This taxonomy is significantly better at reflecting the types of emergent attractors, even beyond sequence prediction, allowing us to classify graphs into ``species" that display similar dynamics. We identified 19 dynamic attractor types that emerge for n <= 5 networks, and classified families of distinct non-isomorphic networks that have identical attractors. In addition to simple limit cycles, we observed more complicated periodic attractors, as well as one n=5 graph with three quasiperiodic attractors and another one with four chaotic attractors.

Disclosures: **K. Morrison:** None. **C. Parmelee:** None. **S. Moore:** None. **C.P. Curto:** None.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.01/VV89

Topic: I.06. Computation, Modeling, and Simulation

Support: DARPA Contract No. HR0011-17-C-0026

Title: Entropy based graph theory models of hydra regeneration

Authors: *S. BATIR, J. LOVAS, R. YUSTE
Dept of Biol. Sci. and Neuroscience, Neurotechnology Ctr., Columbia Univ., New York, NY

Abstract: Hydra vulgaris, a freshwater polyp and member of the phylum Cnidaria, is a representative of the simplest nervous systems in evolution and is also well known for its ability to reconstitute itself following traumatic damage and injury, even re-aggregating its body from a collection of dissociated cells. We are using Hydra as a preparation to both engineer its neural controllers and behavior, and to computationally model and understand its regenerative behaviour. A common assumption in the field has been that a temporal, cause-effect system can sufficiently capture the macro-scale initiation of regenerative behaviour. Here, we have chosen to instead examine time-invariant properties, applying graph theoretic approaches to interpret the evolution of a Hydra's entire neural net during reaggregation. We analyzed calcium imaging movies of transgenic GCAMP Hydra that were actively regenerating, and generated a time invariant graphical model that examines mutual information throughout multiple re-aggregation trials. The graph's vertices are defined as the fluorescent nerve net cells, and the graph's edges are defined as the mutual information across all time points. When we established a mutual information threshold, we observed an underlying, recursive geometry to an actively regenerating Hydra's nerve net. Simple network motifs repeatedly activate across all regeneration trials, recruiting surrounding network motifs in a spreading manner. We further determine underlying geometries of the network's most common motifs, and explore the graph model's balance by maximizing underlying graph entropy while minimizing enthalpy for the formation of new subgraphs within the network. Our analytical approach provides both a time invariant and interdisciplinary paradigm for describing and analyzing nerve-net mediated regenerative behaviour. Through our entropy-graph model of Hydra regeneration, we borrow organizing principles from information geometry and statistical thermodynamics to deconvolve an otherwise complex behaviour that has since eluded biologists and neuroscientists.

Disclosures: S. Batir: None. **J. Lovas:** None. **R. Yuste:** None.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.02/VV90

Topic: I.06. Computation, Modeling, and Simulation

Title: Dynamic network analysis, an application to *C. elegans*

Authors: *V. GEORGE, F. PUPPO, G. A. SILVA
Bioengineering, UC San Diego, La Jolla, CA

Abstract: The complexity of neuronal networks makes it generally intractable to track all actualized signalling pathways. We constructed a geometric graph and analysed the resulting dynamics on that graph through the lens of refractory dynamics. As a proof of concept of our approach, we used the vast trove of C. Elegans research from Worm Atlas to construct a directed

geometric graph and to analyse the resulting dynamics supported by the connectome.
We developed a mathematical framework to analyse the temporal and spatial evolution of signalling in geometric network consisting of nodes (neurons) and edges (axons). To analyse the dynamical evolution of signals in the network we used generally prescribed values for the refractory periods and signalling speeds. For this work we developed tools which allowed us to interrogate the dynamics resulting from a single impulse input to the chemosensory ASEL neuron. Firstly, to get a network level view of the resultant activity we generated a spike raster. We then probed deeper into how the underlying graph supports network activity. Thanks to our approach, and given our access to the connectome, we were able to establish causal links between node activations. Through the capture of the causal links in the system, we established the transient and persistent dynamics supported by the connectome. Additionally, we detected cycles which maintain the persistent activity in the network. Our approach and analysis techniques serve as the basis to experimentally test activation pathways, elucidate pattern generators of the network, and begin to provide a methodology to hypothesize sub-circuits involved in certain functions based upon the prevalent signalling pathways involved in the activation of nodes of interest.
This efficient approach to analyse network dynamics which focuses on the essential signalling characteristics (signalling speeds, delays, and refractory periods) of dynamics within a neural network gives us the ability to probe the activity supported by connectomes. Our preliminary observations during the course of this work raise several theoretical and experimental questions. For example, what is appropriate stimulation protocol with which to perturb the C. Elegans network? Since in this work we focus on food stimulus, how do the patterns of activity compare to different stimuli? For example, touch response. How do gap junctions affect the network behaviour? How best to model a hybrid of spike-time and amplitude modulated networks? In addition to analysis, we also believe more work in signalling characterization of the individual neurons themselves would lead to more robust analysis.

Disclosures: **V. George:** None. **F. Puppo:** None. **G.A. Silva:** None.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.03/VV91

Topic: I.06. Computation, Modeling, and Simulation

Support: Innovation Fund Denmark grant: EXMAD

Title: Wide-field imaging of magnetic fields from brain slice using nitrogen-vacancy centers in diamond

Authors: *M. KARADAS[1], A. M. WOJCIECHOWSKI[2], A. HUCK[2], U. L. ANDERSEN[2], N. O. DALBY[3,2], A. THIELSCHER[1,4]
[1]Electrical Engin., [2]Dept. of Physics, Tech. Univ. of Denmark, Kgs Lyngby, Denmark; [3]Dept. of Drug Design and Pharmacol., Copenhagen Univ., Copenhagen, Denmark; [4]Danish Res. Ctr. for Magnetic Resonance, Copenhagen Univ. Hosp. Hvidovre, Hvidovre, Denmark

Abstract: We explore the feasibility of wide-field imaging of magnetic fields caused by neural activity in rat brain slices with high spatial and temporal resolution using nitrogen vacancy (NV) defects in diamond. Our goal was to determine the required measurement sensitivity and resolution in space and time of the NV sensors. We simulated the magnetic fields using realistic models of pyramidal neurons in the hippocampal CA1 region that would result from evoked events generated by stimulating Schaffer collateral axons. In that setting, excitatory synaptic inputs at AMPA synapses are activated at the stratum radiatum and stratum oriens of pyramidal neurons. The thickness of the simulated brain slice was set to 400 µm, which is similar to standard hippocampus samples prepared for electrophysiological experiments. The calculation of the transmembrane potential and currents was performed using the NEURON (v7.4) software package. Then, the extracellular fields were determined in the diamond plane placed directly below the brain slice. The simulation results demonstrate: (i) The magnetic field vector has one vanishing component that is parallel to the main orientation of the CA1 cells, which is a consequence of the total net axial current density. (ii) If the stimulation is strong enough to generate population spikes in CA1, then the amplitude of the total magnetic field reaches 2.5 nT for the stratum radiatum region, and the temporal information is contained mostly within the DC-0.5 kHz bandwidth. (iii) If the stimulation does not trigger spikes, the field strength and bandwidth reduce to 0.4 nT and 150 Hz, respectively. (iv) Optimal reconstruction of the current source density requires a measurement resolution of around 10 µm. These results suggest that magnetic fields caused by neural activity may be imaged using high-purity diamond sensors with a large NV concentration, combined with a fast, high signal-to-noise ratio camera, commonly used for voltage-sensitive dye imaging.

Disclosures: M. Karadas: None. **A.M. Wojciechowski:** None. **A. Huck:** None. **U.L. Andersen:** None. **N.O. Dalby:** A. Employment/Salary (full or part-time):; Technical University of Denmark. **A. Thielscher:** A. Employment/Salary (full or part-time):; Danish Research Center for Magnetic Resonance.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.04/VV92

Topic: I.06. Computation, Modeling, and Simulation

Title: Implementation of artificial vision for behavioral tests in rats

Authors: *R. BELTRAN-RAMIREZ[1,2], C. VENTURA- MEJIA[2], M. CERPA GALLEGOS[2], E. ARCINIEGA VÁZQUEZ[2], J. ESPINOZA - JR.[2], R. ZEPEDA-GOMEZ[1], J. MARTINEZ-MENDOZA[2], S. CONTRERAS-DELATORRE[2], C. GONZALEZ-SANDOVAL[2], R. MACIEL-ARELLANO[1], V. LARIOS- ROSILLO[1]
[1]Sistemas de Informacion, Univ. De Guadalajara, Zapopan, Mexico; [2]Ctr. de Enseñanza Técnica Industrial, Guadalajara, Mexico

Abstract: Behavioral tests are one of the most important tools for the study of memory and learning, which is used in animal models allowing a better understanding of the behavior of external stimuli, as well as the evaluation of drugs and their effect on the Central Nervous System (SNC).This type of test is divided into 2 large groups, the animal models of conditioned response (4-dish test, conditioning of ultrasonic vocalizations, electrical stimulation of the brain, among others) and unconditioned response (open field, high cross maze, Etc.). In this article we will discuss the Open Maze of Barnes (LAB), which is among the unconditioned response models replacing the Morris water maze avoiding the stress that the test generates on the animal. The LAB is based on the observation of specific behaviors, present in exposed animals in different situations. In these cases we try to provoke curiosity and / or fear of the animal by manipulating the environment, causing the need to hide from the source of what the specimen considers a potential danger [1] [2] [12].Since 1979, when the LAB was developed by Carol Barnes, tests were performed manually, only with the record from an observer, which recorded the data, with the objective of evaluating memory and learning mechanisms.With the development of technology and the advancement of the techniques of Artificial Vision (VA) and image processing (PI), there has been a series of applications and an infinity of uses for this type of processes, from security cameras, to Automatic processes in manufacturing companies.Thanks to the wide field of work and the flexibility of application that has today the computational processing, we decided to integrate it in the existing models for cognitive and behavioral tests.The development of our system focuses mainly on the optimization of the process involved in this type of studies, allowing a greater agility at the time of gathering and processing information and, in turn, allow the interpretation of the results in a shorter period, in addition to Be a low cost tool. Currently there is specialized software for the automation of behavioral tests, however, the cost is high, out of the economic reach of some, and in some cases work specifically with a platform with pre-established characteristics.

Disclosures: R. Beltran-Ramirez: None. **C. Ventura- Mejia:** None. **M. Cerpa Gallegos:** None. **E. Arciniega Vázquez:** None. **J. Espinoza - Jr.:** None. **R. Zepeda-Gomez:** None. **J. Martinez-Mendoza:** None. **S. Contreras-Delatorre:** None. **C. Gonzalez-Sandoval:** None. **R. Maciel-Arellano:** None. **V. Larios- Rosillo:** None.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.05/WW1

Topic: I.06. Computation, Modeling, and Simulation

Support: BBSRC Grant BB/L000814/1

Title: Structural properties of a probabilistic model of neuronal connectivity in a simple vertebrate animal

Authors: *A. FERRARIO, R. MERRISON-HORT, R. BORISYUK
Plymouth Univ., Plymouth, United Kingdom

Abstract: Understanding the relationship between structure and function of neural circuits is a key problem in modern neuroscience. Although the connectivity of neuronal circuits varies considerably between individuals, functional behaviours are approximately the same, especially in the case of simple animals. This commonality in behaviour suggests that there are some fundamental principles that underlie the structure of nervous system. How can we identify these fundamental properties that are shared across individuals and allow the nervous system to function correctly?
We attempt to answer this question in the case of the hatchling *Xenopus* tadpole by defining a probabilistic model (PM) of connectivity between neurons in the animal's spinal cord. The model is derived by generalizing from multiple biologically realistic computer-generated connectomes, each representing a single individual. The model reflects properties that are shared across multiple tadpoles, and they are not biased by the individual differences. We therefore believe that the PM reflects the fundamental organisational principles of neuronal connectivity in this system. We map the connectomes generated by the PM to functional models of spiking neurons to clarify the relationship between structure of connectivity and function (swimming). We use the PM to calculate various structural measures of the whole tadpole spinal network, as well as different functional subnets (e.g. sensory pathway, central pattern generator), and compare these with known measures from other animals: C. elegans, macaque, cat and zebrafish. It is known that these networks can characterised as small-world graphs with hub structures. Similar to that we find that connectomes, corresponding to simulation of the individual tadpole, can be characterised as small-world graphs with hubs. However, this property is removed by the generalization process, as connectomes generated by the PM do not contain hubs. Since these connectomes still swim reliably, we conclude that the presence of hubs is not important for swimming.
Studying the network on one side of the tadpole spinal cord we find that this sub-network is of the small-world type and there are some similarities with C. elegans network. This result makes

an interesting link between the network structure of invertebrates and vertebrates. We calculate the spectrum of network building blocks (motifs) and identify those that are over-represented. We compare these results with similar motifs in C. elegans, macaque and cat cortex as well as the sensorimotor pathway of zebrafish. According to this analysis, the closest correspondence was between the tadpole and zebrafish.

Disclosures: A. Ferrario: None. **R. Merrison-Hort:** None. **R. Borisyuk:** None.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.06/WW2

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF IIS-1524647

Title: A CPG-driven neuromechanical model of forward locomotion in *C. elegans*

Authors: *E. OLIVARES[1], E. J. IZQUIERDO[1,2], R. D. BEER[1,2]
[1]Cognitive Sci. Program, [2]Sch. of informatics and Computing, Indiana Univ., Bloomington, IN

Abstract: Despite the relative simplicity of *C. elegans*, its locomotion machinery is not yet well understood. *C. elegans* locomotes in an undulatory fashion, generating thrust by propagating dorsoventral bends along its body. Two hypotheses have been proposed for the generation of these body bends: central pattern generators (CPGs) and oscillations through sensory feedback from stretch receptors. Calcium imaging studies have established that oscillatory patterns are present in ventral cord motoneurons during both forward and backward locomotion. In a recent study, we used computational modeling to demonstrate that a ventral cord CPG is feasible given the neuroanatomy and neurophysiology of the worm. We identified a repeating neural subcircuit capable of producing a pattern of neural activity that is consistent with what has been observed in the worm during backward and forward locomotion. In this study, we demonstrate that the subcircuit identified in our previous study can be interconnected as a set of repeating neural units along the ventral cord to drive forward locomotion on agar. In order to do this, we integrated the neural model with a reconstruction of a biomechanical model of the worm's body from published descriptions, with updated musculature. We used an evolutionary algorithm to fit the unknown physiological parameters of neurons, synapses and neuromuscular junctions to match the mean velocity observed in worms crawling on agar. We show that it is possible for the worm to locomote forward relying exclusively on ventral cord CPGs, without the use of stretch receptors. While the worm does use stretch receptors, our results suggest the worm is capable of producing realistic movement through multiple CPGs interconnected along the ventral cord. By running the evolutionary algorithm multiple times, we obtained not just one hypothetical solution but an

ensemble of different parameter configurations that allow the model to produce forward locomotion. Analysis of the ensemble allows us to produce testable hypotheses about the neural basis for forward locomotion in the nematode. Altogether, we provide an existence proof for forward locomotion through CPGs in an up-to-date neuromechanical model of the worm, as well as a series of testable hypotheses about its operation.

Disclosures: E. Olivares: None. **E.J. Izquierdo:** None. **R.D. Beer:** None.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.07/WW3

Topic: I.06. Computation, Modeling, and Simulation

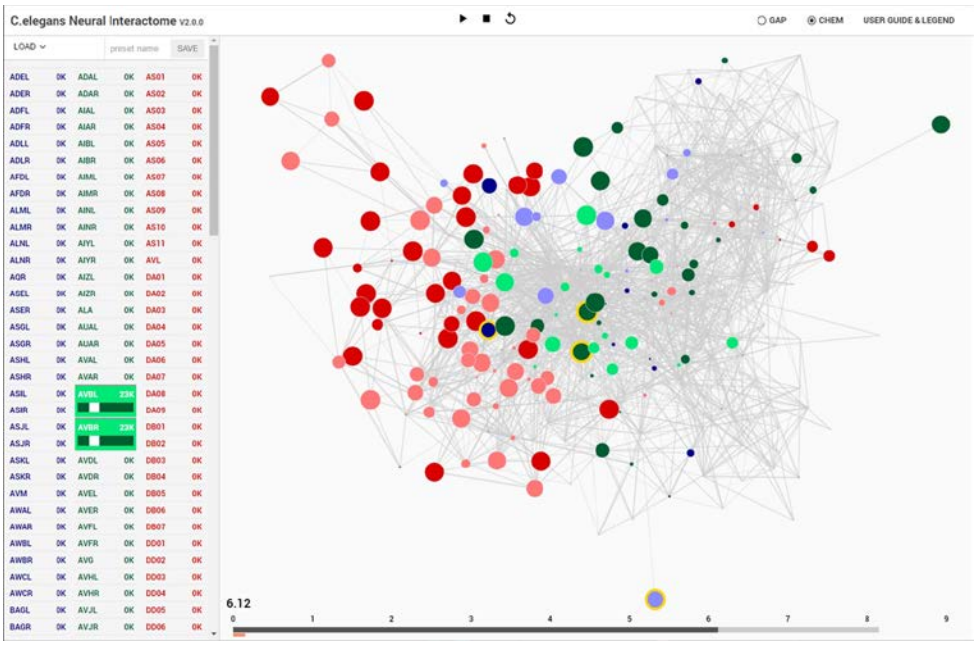
Support: NSF DMS 1361145

Washington Research Foundation

Title: *C. elegans* Neural Interactome: Interactive visualization of a full neuronal system

Authors: J. KIM[1], *E. SHLIZERMAN[2]
[1]Electrical Engin., [2]Univ. of Washington, Seattle, WA

Abstract: Both connectivity structure and dynamical biophysical processes determine the functionality of neuronal networks. We therefore develop a real-time framework, called Neural Interactome, to simultaneously visualize and interact with the structure and dynamics of such networks. Neural Interactome is a cross platform framework implemented in Python and is also a Web interface available online. It combines graph visualization with simulation of neural dynamics, or experimentally recorded multi neural time series, and allows application of stimuli to neurons for examining responses of the network. In addition, Neural Interactome supports structural changes, such as disconnection of neurons from the network (ablation feature), as typically done in experiments. Neural dynamics can be explored on a single neuron level (using a zoom feature), back in time (using a review feature) and recorded (using presets feature). We implement the framework to a model of the nervous system of *Caenorhabditis elegans (C. elegans)* nematode, and show that it can assist in studying neural response patterns associated with locomotion and other stimuli. In particular, we demonstrate how stimulation and ablation help to identify neurons, which play critical role in dynamics related to experimentally studied touch response circuit, and explore new scenarios that did not undergo extensive experimental studies.



Disclosures: **J. Kim:** None. **E. Shlizerman:** None.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.08/DP14/WW4 (Dynamic Poster)

Topic: I.06. Computation, Modeling, and Simulation

Support: Simons Foundation

Title: Network models of zebrafish whole-brain cell-resolution dynamics

Authors: ***M. RUBINOV**, Y. MU, D. V. BENNETT, N. VLADIMIROV, M. B. AHRENS
Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA

Abstract: Cell-resolution calcium-imaging data in zebrafish represent an unmatched view into vertebrate brain activity, but have been little analyzed quantitatively at the whole-brain level. We developed novel constrained factorization algorithms to analyze and model individual cell activity in these data in terms of a small number of interacting functional systems. Unlike many common dimensionality reduction algorithms, our framework produces anatomical representations of functional systems, and allows to interrogate these systems with follow-up ablation and stimulation experiments. The first step in our framework is the conversion of raw pixel time series (with dimensions: ~50 million pixels × ~10 thousand time points) into cell time series. We accomplished this with a combination of volumetric registration, four-dimensional

data storage, and constrained matrix factorization applied to contiguous blocks of these data in parallel. The resulting cell representation of whole-brain activity accurately reproduced the raw pixel time series (Figure 1 [left figure]), while reducing the size of the original data by two orders of magnitude (to ~100 thousand detected cells). We proceeded to factorize the cell time series into brain networks or systems, defined as groups of cells with similar activity. We applied non-negative matrix factorization to whole-brain cell resolution data to detect 10-100 systems, and standardized the spatial representation of these systems across multiple fish (Figure 2 [right figure]). This resulted in the delineation of spatial consensus networks and their associated time series in each fish. Finally, we devised novel nonparametric models to describe the activity of each cell in terms of a small number of overlapping functional systems. This allowed us to reduce the dimensionality of the data even further, and at the same time yielded insights on the activity of individual cells embedded in distinct systems. Together our approach allows a novel understanding of vertebrate whole-brain activity as an empirically constrained and integrated system.

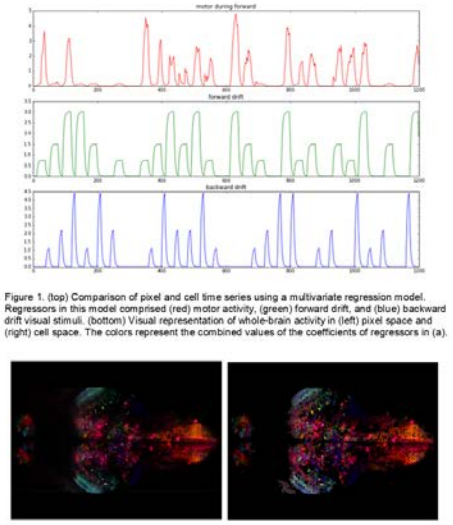


Figure 1. (top) Comparison of pixel and cell time series using a multivariate regression model. Regressors in this model comprised (red) motor activity, (green) forward drift, and (blue) backward drift visual stimuli. (bottom) Visual representation of whole-brain activity in (left) pixel space and (right) cell space. The colors represent the combined values of the coefficients of regressors in (a).

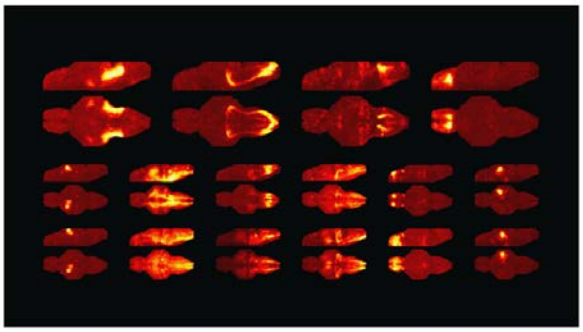


Figure 2. An illustration of 16 systems detected across 6 fish registered to a common template. These systems span the forebrain, midbrain and hindbrain, and include a combination of sensory, motor and associative areas.

Disclosures: **M. Rubinov:** None. **Y. Mu:** None. **D.V. Bennett:** None. **N. Vladimirov:** None. **M.B. Ahrens:** None.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.09/WW5

Topic: I.06. Computation, Modeling, and Simulation

Title: Multi-timescale hidden state modelling of rat behavior reveals temporal-spatial patterns

Authors: *H. SHAN, P. MASON
Dept. of Neurobio., Univ. of Chicago, Chicago, IL

Abstract: Rat locomotion in experimental contexts is widely interpreted for a variety of neuroscientific investigations, often via standardized behavioral tests (e.g. Open Field) or customized paradigms. However, analysis of behavior in these contexts largely relies on human intuition, relying on observers to design metrics or sometimes to score the behaviors themselves. We propose a framework for unbiased, quantitative investigation of rat locomotion activities, using an innovative cross-timescale hidden state discovery approach based on hidden Markov models (HMM). Our approach allows automatic and simultaneous identification of microscopic behavioral modes and macroscopic behavioral strategies. We first show that rat locomotion is computationally low dimensional and composed of stereotyped behavioral modes *at different timescales*, therefore suitable for our approach. Mode usage, and the transition between modes are functions of space and time. Importantly, modes across different timescales are connected to each other in specific patterns that suggest different low-timescale mode usage for different high-timescale locomotion strategies. In addition, the modes, the transition structure and the cross-timescales connections are sensitive to experimental manipulation. We contend that our approach can accelerate experimental investigations of rat behaviors by identifying stereotyped modes automatically and discovering how they are used by global behavioral strategies.
Experimentalists can design behavioral paradigms and metrics in analysis that are informed by stereotyped behaviors in rats. Further, these modes may be driven by distinct circuits and neural network dynamics in the nervous system, offering a way to connect behaviors to neural activities directly.

Disclosures: H. Shan: None. **P. Mason:** None.

Poster

720. Simple Biological Models for Neurocomputational Analysis

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 720.10/WW6

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF IIS-1524647

Title: Integrated neuromechanical model shows stretch-reception can generate and propagate wave responsible for forward locomotion

Authors: *E. J. IZQUIERDO[1,2], R. D. BEER[1,2]
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Abstract: With only 302 neurons and a fully-reconstructed neural and muscle anatomy at the *C. elegans* is an ideal candidate organism to study behavior with the help of computational models. Of particular interest is understanding the neuromechanical basis of locomotion, since nearly its entire behavioral repertoire is expressed through movement. How the rhythmic pattern is generated and propagated along the body is not yet well understood. We report on the development and analysis of a model of forward locomotion that integrates known neuroanatomy, neurophysiology and body mechanics of the worm. Our model is the first to consider recent experimental analysis of the structure of the ventral cord circuitry and the effect of local body curvature on nearby motorneurons. We developed a neuroanatomically-grounded model of the ventral nerve cord subcircuit, using a neural model capable of reproducing the full range of electrophysiology observed in *C. elegans* neurons. We integrated the neural model with a biomechanical model of the worm's body from published descriptions, with updated musculature and stretch receptors. Unknown parameters were evolved using a genetic algorithm to match the speed of the worm on agar. We performed 100 evolutionary runs and consistently found electrophysiological configurations that reproduced realistic control of forward movement. The ensemble of successful solutions reproduced key experimental observations that they were not designed to fit, including the curvature profile of the body's movement, the wavelength, and frequency of the propagating wave. Analysis of the ensemble revealed forward locomotion is possible without intrinsic oscillations in either the head or the rest of the ventral nerve cord. Circuits were capable of initiating oscillations in the head using stretch reception. Similarly, circuits relied on stretch reception to propagate the dorsoventral oscillation, without the need for bistability in the motorneurons, as had been previously proposed, and with gap junctions across neural units playing only a minor role. Altogether, we provide an existence proof for forward locomotion through stretch-reception in an up-to-date neuromechanical model of the worm, as well as a series of testable hypotheses about its operation.

Disclosures: E.J. Izquierdo: None. **R.D. Beer:** None.

Poster

721. Software Tools II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 721.01/WW7

Topic: I.07. Data Analysis and Statistics

Support: NSF Award Number 1516527

the UC Berkeley Office of the Vice Chancellor for Research

Title: Implementation of a query language to enable searching structured neurophysiology data

Authors: *P. JEŽEK, J. TEETERS, F. SOMMER
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Abstract: To standardize the format of contributed datasets, the Neurodata Without Borders: Neurophysiology (NWB) format was developed. The NWB format provides a standardized, yet extendable way to store neuroscience data sets. It includes a self-describing specification language that facilitates annotation of data in a unified way.
To make datasets in NWB format searchable, we developed a query engine to support searching collections of NWB files within a lab or in a repository. The query language implements basic logical, arithmetical and relational math operators. Further, the query engine contains a query parser and an NWB connector. The parser translates a query into an internal tree structure. A NWB connector was created that relates the internal representation of the query to NWB files and returns a serialized result. The NWB connector ensures an abstraction of a native HDF application interface. Technically, it is implemented on top of HDFql language that extends e. g. by filters and logical operations.
In this work we demonstrate the capabilities of the query language in a particular use case, NWB datasets in the CRCNS.org repository. CRCNS.org is a public repository for sharing neurophysiology datasets that are transferred to NWB gradually.
Our long-term goal is to provide a search engine that works across different technologies how to work with neurophysiology data.To achieve this, the query engine is implemented in a modular structure, which facilitates its adaptation to other environments, for example, other search engines and data formats. Specifically, the engine designed to be able to deal with different semantic expressivity of technologies used for neurophysiology data.

Disclosures: P. Ježek: None. **J. Teeters:** None. **F. Sommer:** None.

Poster

721. Software Tools II

Location: Halls A-C

Time: Wednesday, November 15, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 721.02/WW8

Topic: I.07. Data Analysis and Statistics

Title: Harmonization of cortical thickness measurements across scanners and sites

Authors: *N. CULLEN[1], J.-P. FORTIN[2], Y. I. SHELINE[3], R. SHINOHARA[2]
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Abstract: Introduction: With the proliferation of multi-site neuroimaging studies there is a greater need for handling non-biological variance related to the properties of MRI scanners and scan site. Such unwanted sources of bias and variability are typically included as standard confound variables, or confounders, in statistical analyses. However, non-biological confounders

typically have *a priori* unpredictable effects which may compromise the generalizability and reproducibility of results, suggesting the need for statistical methods that harmonize structural neuroimaging data across sites without compromising true biological signal.
Methods: Structural MRI images we acquired from 187 patients with major depressive disorder (MDD) at 4 different sites, with approximately even distributions of age and symptoms across sites. The ANTs cortical thickness pipeline was applied to extract cortical thickness from 102 brain regions in the OASIS template. The ComBat algorithm was applied as a pre-processing step to the cortical thickness values, after which various statistical learning tasks were carried out to understand the relationship between cortical thickness and phenotypic measures.
Results: Before Combat harmonization, median subject cortical thickness significantly differed across sites ($p = 3.3 \times 10^{11}$), particularly at one of the sites, and found 62 individual ROIs significantly associated with site after multiple comparisons. We also found that a cross-validated SVM achieved 76.6% accuracy in classifying the scanning site from their cortical thickness data alone. After applying Combat, median cortical thickness showed no difference across site, nor did any ROIs. Additionally, an SVM trained on Combat-corrected data achieved no better than random chance in classifying subjects by site. Finally, Combat improved associations between cortical thickness and age; the percentage of variation in average cortical thickness explained by age increased from 23 % to 33% before and after Combat, respectively.
Conclusions: Our results suggest that applying the ComBat algorithm to multi-site cortical thickness pipeline removes unwanted non-biological signal, increases univariate associations between regional cortical thickness and phenotypic measures, and increases the strength of out-of-sample multivariate predictions as compared to residual harmonization, adjusted residual harmonization, and the baseline of no harmonization. Most importantly, the ComBat algorithm can be seamlessly dropped into any existing pipeline as a fast and effective pre-processing step.

Disclosures: **N. Cullen:** None. **J. Fortin:** None. **Y.I. Sheline:** None. **R. Shinohara:** None.

Poster

721. Software Tools II

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Support: International Foundation for Research on Paraplegia funding (chair Alain Rossier) to AH

SNF grant 331003A_153448 to AH

SNF grant CRSII3-154453 to AH

Title: Analyzing volumetric anatomical data with immersive virtual reality tools

Authors: *S. PAGÈS[1,2], A. HOLTMAAT[1], J. DONOGHUE[2], G. REYMOND[2]
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Abstract: Recent advances in high-resolution 3D imaging techniques allow researchers to access unprecedented amounts of anatomical data of brain structures. In parallel, the computational power of commodity graphics cards has made rendering billions of voxels in real-time possible. Combining these technologies in an immersive virtual reality system creates a novel tool wherein observers can physically interact with the data. We present here the possibilities and demonstrate the value of this approach for reconstructing neuroanatomical data. We use a custom built digitally scanned light-sheet microscope (adapted from Tomer et al., Cell, 2015), to image rodent clarified whole brains and spinal cords in which various subpopulations of neurons are fluorescently labeled. Improvements of existing microscope designs allow us to achieve an in-plane submicronic resolution in tissue that is immersed in a variety of media (e. g. organic solvents, Histodenz). In addition, our setup allows fast switching between different objectives and thus changes image resolution within seconds. Here we show how the large amount of data generated by this approach can be rapidly reconstructed in a virtual reality environment for further analyses. Direct rendering of raw 3D volumetric data is achieved by voxel-based algorithms (e.g. ray marching), thus avoiding the classical step of data segmentation and meshing along with its inevitable artifacts. Visualization in a virtual reality headset together with interactive hand-held pointers allows the user with to interact rapidly and flexibly with the data (highlighting, selecting, slicing, zooming etc.). This natural interface can be combined with semi-automatic data analysis tools to accelerate and simplify the identification of relevant anatomical structures that are otherwise difficult to recognize using screen-based visualization. Practical examples of this approach are presented from several research projects using the lightsheet microscope, as well as other imaging techniques (e.g., EM and 2-photon).

Disclosures: S. Pagès: None. **A. Holtmaat:** None. **J. Donoghue:** None. **G. Reymond:** None.

Poster

721. Software Tools II

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Program#/Poster#: 721.04/WW10

Topic: I.07. Data Analysis and Statistics

Support: NIH Intramural Research Program (NIDDK)

Title: Open-source group feeding experimentation device (g-fed): Monitoring home cage feeding behavior in rodents

Authors: *M. A. ALI[1], K. P. NGUYEN[3], A. V. KRAVITZ[1,2]
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Abstract: Monitoring food intake is essential for studying eating disorders, however, current methods are either expensive and requires special caging, or cheap and inaccurate. We designed a device called Feeding Experimentation Device (FED), which is a home cage compatible food dispenser that monitors mice feeding behavior with high precision and temporal resolution. FED is cheap and easy to assemble using off the shelf components. FED has an infrared sensor that constantly monitors the presence of a food pellet, where a retrieval of the pellet triggers a motor to dispense a new one. Previously, FED logged the pellet retrieval date and time to a Secure Digital (SD) card. The data could then be analyzed and visualized using a desktop computer. Recently, we have updated FED with two new features: 1) WIFI enabled processor to send data over the internet; this allows for a real time visualization of mice feeding behavior and warning notifications if the device fails to operate, 2) a Radio Frequency Identification (RFID) system to differentiate between individual mice within a single cage for group feeding experiments. These modifications allow greater flexibility in food intake experiments with less intervention from the experimenter. G-FED is an open source, high throughput feeding device that provides instantaneous feeding analytics for group housed mice.

Disclosures: M.A. Ali: None. **K.P. Nguyen:** None. **A.V. Kravitz:** None.

Poster

721. Software Tools II

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Topic: I.07. Data Analysis and Statistics

Support: NIH grant R01 DC009977

NIH grant T15 LM007056

Title: Integrating molecular markers and gene expression in SenseLab for neuroinformatics-driven discovery

Authors: *M. SURLES-ZEIGLER[1], T. M. MORSE[3], R. A. MCDOUGAL[2], G. M. SHEPHERD[4]
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Abstract: SenseLab (https://senselab.med.yale.edu/) is a collection of Neuronal, Olfactory and Disease Databases whose overall aim is to enhance experimental analysis of brain function. The

Neuronal Databases provide curated data about neurons; these include NeuronDB (https://senselab.med.yale.edu/NeuronDB/) which provides unique tools to enable users to integrate data on membrane properties, receptors, and channels in subcompartments of individual neuron types and ModelDB (https://senselab.med.yale.edu/ModelDB/) which provides published models for simulating the experimental results. To extend NeuronDB to new data, we have recently added molecular markers and gene expression data. For this purpose, we added these properties to a subset of hippocampal cells (cells of the dentate gyrus and regions CA1, CA3, and CA4), and will eventually incorporate them into cells from other brain regions within the database. To accomplish this, we are developing a process where first, Natural Language Processing techniques are applied to the PubMed API (application program interface) results to identify and download article abstracts that meet inclusion criteria after a semantic search from a corpus of related terms. These abstracts then progress to the next stage of analysis, article review. For this stage, we began with abstracts related to normal function; to be extended eventually to disease processes or treatments and developmental. During article review, molecular marker, gene expression data and the associated metadata (e.g. animal species, age, sex) are extracted from journal articles and stored in an EAV/CR (entity-attribute-value with classes and relationships) database. This data is accessible to the user via an expanded NeuronDB, and an interactive hippocampus microcircuit browser. The browser enables interoperability between the SenseLab databases' neuronal properties with links to other properties such as electrophysiological data as tracked by associated databases such as Neuroelectro (http://neuroelectro.org). Furthermore, this combined data is displayed in a new integrated graphic format called microcircuit viewer within the FunctionalMicroconnectomeDB, in which each neuron can be selectively visualized in relation to the different cell compartments and their properties within the microcircuits to which they contribute. Incorporation of molecular markers and gene expression data into the SenseLab databases will accelerate experimental and modeling research, assist in the exploration of experimental studies and models of neurons and their ion channels and receptors.

Disclosures: M. Surles-Zeigler: None. **T.M. Morse:** None. **R.A. McDougal:** None. **G.M. Shepherd:** None.

Poster

721. Software Tools II

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Topic: I.07. Data Analysis and Statistics

Title: Digital signal processing toolbox for real time MEG data analysis in source space

Authors: A. MOISEEV, N. PEATFIELD, S. DOESBURG, T. CHEUNG, *U. RIBARY
Simon Fraser Univ. (SFU), Burnaby, BC, Canada

Abstract: There is a growing interest in analysing MEG data in real time known as real-time MEG (rtMEG). rtMEG has potential applications in training/rehabilitation of patients using neurofeedback, brain-machine interfaces, communicating with patients with locked in syndrome, brain injury diagnostics to name a few. Recent advances in MEG instrumentation allow delivery of the MEG signal to digital signal processing (DSP) systems with sub-millisecond delay from the brain event. Earlier MEG studies showed that the brain can process sensory information in discrete time quanta as small as 12-15 ms (Joliot et al 1994). Thus to be successful, it may be crucial for rtMEG DSP system to submit its output to a feedback loop with milliseconds latency. With this performance objective in mind, we implemented a DSP toolbox to be used with the latest generation of CTF MEG electronics. In addition to basic data buffering and flow control functions, it provides on-the-fly source reconstruction using a SAM beamformer (Robinson & Vrba, 1999). To our knowledge, other existing rtMEG implementations use minimum-norm based global inverse solutions, which allow faster computations at the expense of spatial resolution. In contrast, our toolbox implements high resolution beamformer reconstruction. It was made possible by leveraging multi-threaded parallel processing capabilities of the modern computers. The software is written in C++ and runs on a general-purpose computer under a Linux OS. As an example, for an Intel 7-4820K CPU 3.7 GHz desktop it takes less than 1 ms to reconstruct amplitudes of 100 brain sources using 275 MEG channels input. The toolbox communicates with both the CTF MEG electronics and a client application using TCP-based messaging. The client may run in parallel with the toolbox on the same machine, or on a remote host. As a proof of concept, we used a retinotopic mapping experiment. We presented a subject with 9Hz flickering stimuli to map the differing portions of the visual cortex. The acquired data was replayed at 300 samples per second. We were able to localize both the fundamental and the first-harmonics with less than 50 ms latency across multiple virtual sensors. We will present results of actual rtMEG collections with several subjects based on this paradigm. Support: AMG Global Research Inc., BC LEEF, CFI, CIHR, CTF MEG, NSERC

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Poster

721. Software Tools II

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Title: Robust estimation of calcium transients by modeling contamination

Authors: J. L. GAUTHIER[1], *A. S. CHARLES[2], J. W. PILLOW[3], D. W. TANK[1]
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Abstract: Two-photon calcium imaging has enabled recording of large neural populations, but distinguishing the activity of individual neurons is not always straightforward. In densely stained tissue such as the CA1 region of mouse hippocampus, many cell bodies and processes can overlap in a small space, posing the computational challenge of demixing their signals. Automated “cell finding” methods have been developed to identify the shapes and transients of neural sources, including demixing signals from overlapping sources. These methods, however, remain susceptible to a fundamental problem: unidentified sources can produce signals that contaminate the transient estimation for identified sources. For example, if a neurite overlaps a cell body, but only the shape of the cell body was identified during cell finding, fluorescence activity in the neurite will produce an increase in the estimated fluorescence of the cell body. If unaddressed, contamination can impact scientific conclusions. For example, in one dataset collected from CA1 in an awake, behaving mouse, some pyramidal cells appeared to have multiple place fields, when in fact their time courses included activity from multiple, overlapping neurons, each of which only had a single place field. In this work, we develop an algorithm to remove such false transients. This method is based on modeling the noisy observed movies as consisting of either known sources, or a mixture of known and unknown sources (i.e. neurons or processes not detected during cell finding). We model the unknown sources as a sparse sum of Gaussian shaped dictionary elements, allowing the method to flexibly construct new sources that describe activity not accounted for by the known sources. An approximation to the maximum likelihood estimator was used to infer the activity of the known sources as well as the structure and activity of the unknown sources. This optimization reduces to an efficient and tractable modification of the LASSO procedure. We call this estimator Sparse Emulation of Unknown Dictionary Objects, or SEUDO. When applied to CA1 recordings in which some active neurons were not identified during cell finding, the performance of SEUDO was compared to manual human classification. All true transients were preserved, and false transients were either reduced in amplitude or eliminated entirely.

Disclosures: **J.L. Gauthier:** A. Employment/Salary (full or part-time):; Princeton University. **A.S. Charles:** A. Employment/Salary (full or part-time):; Princeton University. **J.W. Pillow:** A.

Employment/Salary (full or part-time):; Princeton University. **D.W. Tank:** A. Employment/Salary (full or part-time):; Princeton University.

Poster

721. Software Tools II

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Topic: I.07. Data Analysis and Statistics

Support: NIH Grant RO1-NS076772

Title: Selective, subsecond measurement of *In vivo* hydrogen peroxide dynamics employing a double voltammetric waveform

Authors: *C. MEUNIER, E. MITCHELL, V. TOUPS, J. ROBERTS, G. MCCARTY, L. A. SOMBERS
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Abstract: Hydrogen peroxide (H_2O_2) is a reactive oxygen species that also serves as an important signaling molecule in normal brain function. Its concentrations fluctuate with precise spatial and temporal resolution such that functional levels can be achieved for signaling, yet unregulated H_2O_2 generation contributes to a myriad of pathological consequences due to oxidative stress. Studies aimed at elucidating these dynamics and the diverse roles that H_2O_2 plays in complex biological environments have been hindered by the lack of a method for probing dynamic H_2O_2 fluctuations in living systems with molecular specificity. Fast scan cyclic voltammetry (FSCV) at carbon-fiber microelectrodes provides a method of detecting H_2O_2 with high temporal and spatial resolution that can be used in awake and behaving animals. However, H_2O_2 variability can be masked by pH changes, which are common *in vivo*, because the voltammograms for these species overlap. A clear distinction between pure H_2O_2 and pure pH voltammograms is required for regression analysis of mixed voltammetric data. We present a novel method for removing pH contributions from complex voltammetric data. By employing two distinct potential waveforms per scan, one in which H_2O_2 is electrochemically silent and a second in which both pH and H_2O_2 are quantified. Using multivariate analysis with this waveform paradigm permits the quantified of both analytes. Thus, this work provides a powerful tool that has been used to disambiguate and evaluate spontaneous H_2O_2 fluctuations in vivo on a subsecond timescale. The data directly verify a functional relevance for dynamic H_2O_2 signaling in the dorsal striatum.

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Poster

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Title: Designing workflows for the collaborative management and analysis of electrophysiological data and metadata

Authors: J. SPRENGER[1,2,3], A. YEGENOGLU[1,2,3], S. GRÜN[1,2,3,4], *M. DENKER[1,2,3]
[1]Inst. of Neurosci. and Med. (INM-6), [2]Inst. for Advanced Simulation (IAS-6), [3]JARA BRAIN Inst. I (INM-10), Jülich Res. Ctr., Juelich, Germany; [4]Theoretical Systems Neurobio., RWTH Aachen Univ., Aachen, Germany

Abstract: The complexity of neuroscientific experiments and their analysis has grown to a degree where special effort and attention is required to guarantee their reproducibility. In addition, collaborations across different laboratories and countries are becoming a standard work setting, which increases the need for comprehensive documentation of data and metadata, and explicit, formal descriptions of the data analysis process. The availability of software tools that support scientists in the various steps of this process is therefore indispensable [Denker and Grün (2016) In: Brain-Inspired Computing: Brain Comp 2015, Springer]. Moreover, it is necessary to establish the workflows that link the various tools, and to develop simple interfaces for them. Here we demonstrate how such a reproducible, structured, and comprehensible workflow for an electrophysiological experiment, covering the preparation, annotation and analysis data, can be set up in a collaborative environment by the combination of multiple state-of-the-art open-source projects. The workflow features the Electrophysiology Analysis Toolkit (Elephant), which represents the central analysis resource offering methods ranging from the analysis of ensemble spike data to population signals, such as local field potentials [http://neuralensemble.org/elephant/]. Elephant is based on the generic standardized data representation for electrophysiological data provided by the Neo library [Garcia et al. (2014) Front Neuroinf 8:10]. In addition, Neo is able to interface with a range of data formats commonly used in electrophysiology. The open metadata Markup Language (odML) is used as the hierarchical structure to store metadata related to electrophysiological experiments [Grewe et al. (2011) Front Neuroinf 5:16]. Furthermore, odMLtables extends the accessibility of odML by providing an interface to a tabular metadata representation, e.g., using Excel

[https://github.com/INM-6/python-odmltables]. Finally, NIX is a newly developed scheme designed to combine electrophysiological data and metadata in a single, standardized format [https://github.com/G-Node/nix], and links the Neo and odML data models. We discuss multiple mechanisms that allow to describe the workflow itself, and show how it may be implemented, e.g., using the Collaboratory of the Human Brain Project [https://collab.humanbrainproject.eu]. While focusing on electrophysiology, many concepts of this workflow are also transferable to different types of experimental environments.

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Poster

721. Software Tools II

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Program#/Poster#: 721.10/WW16

Topic: I.07. Data Analysis and Statistics

Title: Apes: Automated pipeline for EEG source reconstruction for large scale EEG analysis

Authors: *M. VIRMANI[1], N. AHUJA[2], N. PEGWAL[2], R. SHARMA[2]
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Abstract: Available EEG source analysis softwares lack the automation for source analysis with options of choosing multiple subjects, task conditions, method of inverse solution etc. In pursuit of fixing all the above problems with source code of openly available softwares, the focus of researchers deviates from focussing on the scientific problem to ‘how’ to do EEG data analysis. Automated Pipeline for EEG Source reconstruction (APES) aims to do away with these challenges and provide a streamlined and highly intuitive software to perform source localization with the flexibility to change and compare multiple parameters according to the need of a particular experiment. The pipeline uses MATLAB programming language and the functions of Brainstorm toolbox (which could be extended to other softwares such as Fieldtrip, EEGLAB etc.). APES has incorporated the following order of operations with a possibility to add additional operations: i) Asks user to put standard inputs: Headmodel, Channel file, Subjects EEG data, Anatomy, Choice of source algorithm ii) Extracts all the epochs for each subject’s EEG data, iii) Compute the necessary inputs for the chosen source algorithm, iv) Compute the inverse solution for each epoch, and finally, v) Compute the source waveform for each epoch of each subject. This order of operations could be repeated for any number of conditions and any number of subjects thereafter. As a test, source localization was performed using APES for extracting sources of Default Mode Network in Sternberg Working Memory experiment. APES was performed for 27 subjects, 4 conditions with ICBM152 anatomy, GSN-128 channel and a

headmodel created using Boundary Element Method (BEM). The spatial filtering technique called Beamforming was used as source localization algorithm. APES demonstrated the computation time of 2s per epoch to obtain the inverse solution, which is highly optimized when compared to multiple manual steps required in other softwares. Also it removes difficulties in repeating the similar experiment with slightly different parameters. APES has the potential to become a full-fledged EEG analysis software platform with further enhancement in the extension of the features such as preprocessing, statistical analysis, plotting etc. and using high-performance programming languages like Python/ C++. APES aims to contribute to the mission of democratizing neurotechnology by giving any hacker/ hobbyist as well as researchers to draw significant insights about how our brain works and thus advance the field of neuroscience, with utmost ease.

Disclosures: **M. Virmani:** None. **N. Ahuja:** None. **N. Pegwal:** None. **R. Sharma:** None.

Poster

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Alfred P. Sloan Foundation

Title: Real-time experimental control with graphical user interface (REC-GUI) for neuroscience research

Authors: ***B. KIM**, S. KENCHAPPA, T.-Y. CHANG, L. W. THOMPSON, A. ROSENBERG
Neurosci., Univ. of Wisconsin - Madison, Madison, WI

Abstract: The accurate and precise association of neuronal activity and behavior requires the combination of real-time experimental control, stimulus rendering/presentation, as well as precisely timed measurements of electrophysiological/behavioral responses. Jointly satisfying the design specifications to achieve these distinct requirements is a challenge for experimental control systems. Towards the goal of developing a flexible solution for neuroscience research, we are spearheading a novel framework for conducting high precision experimental control using network-based parallel processing. The Real-Time Experimental Control with Graphical User Interface (REC-GUI) consists of three major components: (*i*) experimenter control, (*ii*) scripts for rendering/presenting experimental stimuli, and (*iii*) data acquisition for behavioral measurements and high-density neural recordings. At the system's core is network-based parallel

processing. Command sets are grouped into two major components: (*i*) experimental control/behavioral monitoring and (*ii*) stimulus rendering/presentation. Each group of command sets is executed on separate CPUs that communicate using internet protocols (UDP/TCP). This flexibly allows each CPU to execute command sets written in different computer languages and across different operating systems, with the only requirement being that they support network interfacing. Network-based parallel processing provides two distinct advantages: (*i*) a modular design that minimizes coding efforts (users can flexibly select the coding language) and (*ii*) high temporal accuracy of stimulus presentation and data acquisition. To demonstrate the rigor of this network-based parallel processing scheme, we implemented the following system: (*i*) experimenter control (Python GUI on Linux), (*ii*) stimulus rendering (MATLAB with PsychToolBox on Linux) and stimulus presentation (PROPixx, VPixx Technologies Inc.), and (*iii*) data acquisition (Scout Processor, Ripple Inc. on Windows). The GUI provides a customizable interface for the manipulation of experimental parameters, offering unique usability with real-time graphical feedback of behavior. We present testing results which confirm that this state-of-the-art system can support highly demanding neuroscience experiments. Because the system is modular, all software and hardware components can be easily substituted to meet specific experimental needs. Sample code and hardware configurations will be made available as a template for system customization.

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Poster

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Topic: I.07. Data Analysis and Statistics

Support: NIH Grant U01NS090569

Title: Particle Tracking based Motion Compensation for neuronal imaging

Authors: *W. LOSERT, S. AGHAYEE, D. WINKOWSKI, P. KANOLD
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Abstract: Calcium Imaging provides a real time view of neuronal activity with single cell resolution, with exciting possibilities for real-time readout of neuronal activity, and the potential to modulate neuronal activity with some feedback control. One challenge that prevents simple real time readout of neuronal activity from calcium imaging is jitter in the image. Since imaging is at the single neuron level, even minute shifts or rotations of the imaging field are detectable. Shifts in the location of neurons can lead to artifacts in the quantification of neuronal activity

from calcium images. Thus motion compensation is essential. We introduce a new technique to carry out Motion Compensation for Calcium Imaging that is derived from particle tracking approaches. Particle tracking based motion compensation uses only the brightest neurons that are scattered throughout an image -ten or less are generally sufficient - and tracks their position from frame to frame. This yields information on the shift in position at about ten points spread throughout in the image, which in turn is used to infer the motion and rotation of the image that best agrees with the shift of all points. This approach thus can compensate for rotational shifts unlike most other tools, and is fast enough for real time motion compensation, real time spike inference analysis, and feedback control. We validate the approach on two-photon calcium images in the superficial layers of auditory cortex of awake mice, with a simple nuclear stain as a second steady fluorescent signal that complements the genetically encoded calcium indicators.

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Poster

721. Software Tools II

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Topic: I.07. Data Analysis and Statistics

Support: NIH grant R44MH108053

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Title: Whole mouse brain cell mapping with anatomic specificity using a standardized atlas

Authors: *N. J. O'CONNOR[1], B. S. EASTWOOD[1], S. J. TAPPAN[1], M. J. FAY[1], S. GERFEN[1], P. J. ANGSTMAN[1], C. R. GERFEN[2], J. R. GLASER[1]
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Abstract: Analyzing cellular populations within specific anatomies in brain images requires expertise in identifying neuroanatomy combined with effective cellular identification. The former typically involves a human comparing experimental images with a reference atlas and manually delineating anatomies in images for cellular population analysis. We have developed automated technology capable of reconstructing a whole brain image from serial sections, aligning this 3D brain image to a reference atlas, delineating anatomies in the experimental space, and detecting cells within these anatomies. Mapping cell populations to a standardized atlas allows researchers to objectively accumulate and compare results.
This technology includes alignment methods for assembling 3D brain images from experimental serial sections that are translated, rotated, and flipped with respect to each other. The platform

also includes registration methods for automatically matching the assembled brains to the Allen Institute for Brain Science's Common Coordinate Framework (CCF, http://mouse.brain-map.org/). Following registration, brain structures can be selected in the reference atlas and automatically delineated in the experimental 3D brain image. Newly developed cell detection methods are then performed within the delineated structures to examine population distribution. For validation, we analyzed both brightfield and fluorescent Nissl stained coronal mouse brain sections in whole slide images. Sections from these images were automatically extracted, aligned, and compiled into full resolution 3D whole-brain images (BrainMaker). The 3D brain images were then automatically registered to the Allen CCF using linear and nonlinear transform optimization. Brain structures were selected and delineated in the experimental images, and automated cell detection was applied within these structures. Validation was performed to assess the accuracy of the automated delineation and cell detection.
Here we introduce improved technology for mapping cellular populations to specific structures in reconstructed whole brain images from serial sections. This technology provides repeatable, objective measures that can be compared across experiments and laboratories. The automation of detection and anatomic mapping of cellular populations also creates the possibility of increasing the efficiency of experimental workflows.

Disclosures: **N.J. O'Connor:** A. Employment/Salary (full or part-time):; MBF Bioscience. **B.S. Eastwood:** A. Employment/Salary (full or part-time):; MBF Bioscience. **S.J. Tappan:** A. Employment/Salary (full or part-time):; MBF Bioscience. **M.J. Fay:** A. Employment/Salary (full or part-time):; MBF Bioscience. **S. Gerfen:** A. Employment/Salary (full or part-time):; MBF Bioscience. **P.J. Angstman:** A. Employment/Salary (full or part-time):; MBF Bioscience. **C.R. Gerfen:** None. **J.R. Glaser:** A. Employment/Salary (full or part-time):; MBF Bioscience.

Poster

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NIDCD R01 DC002852

NIMH P50 DC01027

Title: Using a probabilistic atlas to improve manual parcellation of the cerebellum

Authors: ***A. J. WORTH**[1], J. A. TOURVILLE[2]
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Abstract: In order to develop automated methods for labeling anatomy in MRI brain scans, regions of interest (ROIs) must first be labeled manually and this must be done in a large representative sample in order to capture variability. This is a tedious task that requires considerable expertise but the overall effort can be reduced and the accuracy and reliability can be increased by using a probabilistic atlas to improve both the individual ROIs and also the labeling method.
The cerebellum was labeled in 56 T1-weighted MRI brain scans. There were 31 unique subjects, 25 of which were scanned twice and labeled blind as to which were repeat scans. We also labeled the famous high-resolution Colin27 scan. Following the Schmahmann et al. atlas, 33 regions were delineated in coronal slices: brain stem, right and left cerebellum white matter, and right, left and vermis lobules: I-IV, V, VI, CrusI (vermis "VIIAf"), CrusII, (vermis "VIIAt"), VIIb, VIIIa, VIIIb, IX, X. Identification of the relevant cerebellar sulci was done with the aid of 3D renderings of the cerebellum surface at a series of depths between the white matter and exterior surface. The iso-intensity surfaces were defined by various intensities on either side of the gray matter peak intensity found in a histogram over the cerebellum region. "Sulci lines" drawn on these surface were projected into the 3D scan volume space to identify specific sulci. "Parcellation lines" were then drawn based on the sulci lines in coronal slicess to separate the cerebellar cortex into lobes.
All labeled scans were used to create a probabilistic atlas by averaging the presence or absence of each label after a simple 3D warp to normalize the size of each cerebellum. Then, each region in each slice of every scan was compared to this atlas and an "atlas mismatch" score was calculated. In order to flush out labeling errors, large mismatch values were flagged and those outlines were examined and modified as necessary.
In our results, we describe the locations and types of errors that were found using the probabilistic atlas, and we suggest modifications to the labeling method to improve the reliability and decrease labeling time. In our initial work, we noted the lack of a reliable landmark for dividing vermis VIIAt and vermis VIIAf. According to Schmahmann et al., these regions are separated by the horizontal sulcus. This sulcus is one of the more robust landmarks on the lateral surface but rarely extends medially across the vermal surface. As such, the boundary between these two regions is often arbitrary. Reliable labeling of these areas requires either combining these two small vermis ROIs or identifying another, more robust landmark.

Disclosures: **A.J. Worth:** A. Employment/Salary (full or part-time):; Neuromorphometrics, Inc. **J.A. Tourville:** F. Consulting Fees (e.g., advisory boards); Neuromorphometrics, Inc..

Poster

721. Software Tools II

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Topic: I.07. Data Analysis and Statistics

Title: Real-time, automatic calcium image segmentation via topology

Authors: *M. VAIANA[1], E. M. GOLDBERG[2,3], S. E. MULDOON[4]
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Abstract: We present a new method for automatic segmentation of cells from background in two-photon calcium imaging data using topological image analysis. Specifically, we classify homology cycles resulting from the persistent homology of the image complex. Our method offers the following two improvements over current methods. First, the segmentation is run on a single image instead of an entire movie. This allows a researcher to capture a single image at the beginning of a recording session and segment it immediately in real-time. Second, our method captures both neurons that fire and that do not fire. This is desirable when imaging one spatial region multiple times or over multiple sessions, as neurons which fire in one recording but not another will be registered consistently throughout the dataset. We note that, coupled with improvements in real-time motion correction, our method would allow for real-time analysis of neural dynamics.

Disclosures: M. Vaiana: None. **E.M. Goldberg:** None. **S.E. Muldoon:** None.

Poster

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Topic: I.07. Data Analysis and Statistics

Support: Xpansa Research Fund

Title: How to find candidate drugs to be repositioned for neurodegenerative disorders within a graph of globally connected machine-readable papers?

Authors: *R. GURINOVICH, A. PASHUK, E. MOROZ, Y. PETROVKIY, A. DMITRIEVSKIJ, O. KURYAN, A. TIGGRE, A. SCERBACOV
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Abstract: Drug development is a time and resource consuming process. Luckily, it produces vast amounts of knowledge in the form of laboratory notebooks, grant applications, research papers, and clinical studies reports. Whether the primary goal of the initial project was achieved or not, documented findings can still potentially contribute to future discoveries. Due to the time and economic pressures in de novo drug development, drug repositioning, enabled by this data, is a particularly valuable way of doing discovery.

To make the most from the immense size of the global research communication, research organizations require innovative methods. One of these methods is to decompose research literature to the statements, to link them in the graph and to make new research based on the resulting connections.
This is the method we apply to model a process of drugs repositioning for neurodegenerative disorders. First, we semanticize open access (OA) papers to produce their machine-readable versions through the sci.AI platform. The processed literature is then connected in the graph. The platform performs a search within the graph to find candidate drugs and therapies that might be applied for the treatment of the neurodegenerative disorders. Finally, the results of this computational method are validated against existing research reports.

Disclosures: **R. Gurinovich:** A. Employment/Salary (full or part-time):; sci.AI. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Xpansa. **A. Pashuk:** None. **E. Moroz:** None. **Y. Petrovkiy:** A. Employment/Salary (full or part-time):; sci.AI, Odessa National Medical University. **A. Dmitrievskij:** None. **O. Kuryan:** None. **A. Tiggre:** None. **A. Scerbacov:** None.

Poster

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Topic: I.07. Data Analysis and Statistics

Support: NIH Grant U01 MH105971

Title: Automated reconstruction pipeline for oblique light sheet tomography

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Abstract: Light-sheet fluorescence microscopy (LSFM) provides volume imaging of specimens spanning from a few microns to multiple millimeters of tissue. LSFM has the advantage of high imaging speed, high dynamic range, low photobleaching and low noise. Oblique Light Sheet Tomography (OLST) is one such system tailored specifically for volumetric imaging of larger specimens. This setup combines LSFM, XYZ translation stages and a vibratome-based tissue sectioning to achieve high-speed and constant high-resolution imaging throughout large tissue volumes. In the current application of OLST, a whole mouse brain is imaged at 0.4 microns XY resolution and 2.5 microns Z spacing between oblique planes, in 14 hours.While light sheet ensures an illumination restricted in the thickness (Z of the specimen) of the imaging plane,

fluorescently labeled structures appear broader than they are due to a blur from the optical transfer function of the imaging system, including the Abbe's diffraction limit, NA of the collection objective and camera properties. This blur assumes a Gaussian shape as it comes from a point source. To overcome this constraint, an additional step of deconvolution was added before reconstruction of the image volumes. Deconvolution improves SNR of image pixels by ameliorating the effect of stray fluorescence from XY neighborhood in the illumination plane, such as source autofluorescence, camera artifact, and photon scattering within the tissue.We modelled a 3-D Gaussian point spread function designed to match that of the detected blur using the experimental beam parameters, 5 microns at the center but 20 microns near the edges, and used it for pixel-wise deconvolution. Deconvolution with our generated point spread function resulted in a significant noise reduction and narrower pixel point spread functions. Our technique, using Lucy-Richardson Deconvolution, achieves improved resolution and decreased background, as well as sharper halo-reduced images.The image transformation model used to generate the coronal section series has also been modified. Instead of aligning sections after reconstruction, we now model and apply a shear transform to shear the oblique image stack. Software for image stitching that is specifically suited for an OLST image series was also developed. These enhancements have improved reconstructed image quality and decreased processing time.

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Topic: I.07. Data Analysis and Statistics

Support: NIH RO1NS075366

Title: Semi-automated detection and characterization of spike-wave discharges (SWDs) in a mouse model of absence epilepsy

Authors: *J. A. PFAMMATTER[1], E. P. WALLACE[3], R. K. MAGANTI[4], M. V. JONES[2]
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Abstract: Absence epilepsy is characterized by nonconvulsive seizures, apparent as spike-wave discharges (SWDs) on electroencephalogram (EEG) recordings, that are associated with behavioral arrests, altered consciousness, and amnesia. Detection of SWDs from EEG is traditionally done manually by clinicians and researchers. Manual detection of SWDs is time

consuming, expensive and variable both within and between scorers and between sleep stages within EEG records. These issues present a sizeable roadblock to rapid and unbiased scoring of SWDs. Here we present a semi-automated, machine learning-based method for the scoring of SWDs, implemented on 4-channel, normalized EEG records from mice with absence epilepsy (RQ: knock-ins expressing the GABA-A receptor mutation gamma2R43Q) and wild type littermates (RR). First, we train a support vector machine (SVM) to detect SWD-containing epochs (4 seconds) using a training set of example SWD- and non-SWD-containing epochs that were manually scored by human experts. This SVM uses 29 parameters calculated from EEG records and is designed to detect 'all' events that an expert human would detect at the cost of increased false positives. Automated detection of putative SWD start and stop times is performed by finding ~6 Hz patterns (the typical SWD frequency in mice) in the first derivative and the correlation between an SWD template and the EEG signals. The algorithm scores a 24-hour record in less than 5 minutes whereas manual scoring takes approximately 2-3 hours. A manual review of putative SWDs is still required at this stage, but future versions of the algorithm may only require a spot-check review. Detection of SWDs in data that were not included in training (24 hr records; 3 from 3 RQ animals, 1 from 1 RR animal) revealed a 99.78 % capture rate (of 893 events) and a 1.23 % false-positive rate (of 91065 events) compared to human scoring of the same data. Many false-positive events contain SWD-like features, detection of which scales with the frequency of true SWDs within each record. To improve the algorithm, we are pursuing analysis of the characteristics of SWDs and SWD-like events identified by the algorithm compared to those identified manually. Interestingly, numerous SWDs were found in RR animals both by human scoring and automatic detection.

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Poster

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NIH RO1 EY024067

Title: Automatic segmentation of the primate brain using deep fully-convolutional networks

Authors: *K. BROWN[1], P. VELASCO[2], B. PESARAN[3]
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Abstract: Convolutional Neural Networks (CNNs) have recently been employed with great success in image classification, and increasingly, semantic image segmentation. Despite their popularity, most approaches focus on 2D images, while most medical imaging data consists of 3D volumes. Here we apply a recently developed fully-convolutional network (U-net) architecture for semantic segmentation of human and non-human primate structural MRI voxels into gray-matter, white-matter, and cerebrospinal fluid tissue classes. We show that our model achieves state-of-the-art performance on MRI segmentation tasks, with minimal training time. We train and test our model on two datasets, a rhesus macaque T1-weighted MR images, and a publicly available dataset (MRBrainS). Macaque data were acquired with a 3T Siemens Allegra (Erlangen, Germany) using 3 elements out of a 4-channel phased array from Nova Medical Inc. (Wilmington, MA) and 0.6 or 0.5 mm^2 in-plane resolution, slice thickness: 0.6 or 0.5 mm. For the macaque dataset, ground truth was established by first warping an atlas to the structural scan using a diffeomorphic registration procedure (SyN), then hand-edited by visual inspection. For the MRBrainS dataset, ground truth was established by expert hand labeling.
Our deep convolutional architecture consisted of an expanding and contracting path, applied to 3D patches of the structural MRI volume. Each convolutional block is realized as a residual function composed of convolutions with a 3x3x3 voxel kernel followed by a skip connection consisting of an identity mapping and a summation. Between each block in the contracting path, the image is downsampled via 2x2x2 convolutions with a stride of 2. Empirical Linear Units are used throughout the network. In the expanding path, residual blocks are upsampled via a deconvolution with a stride of 2. The output of the contracting path of equal resolution is merged via a skip connection to the output of the expanding path by concatenation. In this way, detailed information from each stage of the contracting path is paired with higher-level representations. The final layer consists of 1x1x1 convolutions with a sigmoid activation indicating the probability of belonging to the segmentation mask.
Segmentation of primate neuroanatomy from MR images into tissue classes forms the basis of several measurements such as gray-matter volume or cortical surface generation. Such measurements form the core of many studies, including voxel-based morphometry and surface-based functional MRI studies. The success of learning segmentations suggests a similar approach may be viable in other imaging domains such as diffusion-weighted MR imaging.

Disclosures: **K. Brown:** None. **P. Velasco:** None. **B. Pesaran:** None.

Poster

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Title: Defining and assessing the integrity of cortical layering: A quantitative approach

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Abstract: The architecture of the human neocortex consists of cellular columns that traverse six cortical layers. Objective methods have been developed for the definition of cortical columns (Buxhoeveden, Switala, Roy, & Casanova, 2000); however, the definition of transitions between cortical layers largely relies on subjective methodology. It was the intent of the current project to create an objective method that could both identify cortical transitions between layers, and then assess the transition's integrity in Nissl stained tissue. To this end, a modified edge detection method capable of accounting for the convoluted nature of the human cortex was developed to identify the transition between cortical layers I & II. Further, after defining the cortical transition, assessment of the transition's integrity was made by obtaining a measure of sinuosity. This measure calculates the ratio of the identified transition length by the Euclidean distance of a hypothetical linear transition. This method has the potential to objectively quantify the cortical transition between layers I & II as well as assess the nature of the transition. This allows for the collection of objective data pertaining to abnormalities resulting from pathological processes involved in cortical development.

Disclosures: A.T. Karst: None. **J. Berger:** None. **J.J. Hutsler:** None.

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Support: This work was funded by the Allen Institute for Brain Science. The authors wish to thank the Allen Institute for Brain Science founders, Paul G. Allen and Jody Allen, for their vision, encouragement, and support.

Title: Building a prototype application for visualizing neuroanatomy and quantitative cell features from the Allen Brain Atlas in virtual space

Authors: *A. BERNARD[1], B. BLANCHARD[1], F. LEE[1], T. DOLBEARE[1], N. GRADDIS[1], D. TOLOUDIS[2], N. GOUWENS[1], D. FENG[1], L. NG[1], C. KOCH[1]
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Abstract: Effective visualization of neuroscientific data can be difficult; complexity can mask trends, scale is easy to misunderstand, and highly dimensional data is challenging to present in a simple way that retains content. Virtual Reality (VR) is uniquely positioned to improve depth

and comprehensibility of data visualization. We sought to explore the use of VR for its potential to improve upon conventional presentation of complex 2D data, and to evaluate this emerging technology as a means to inspire a new cohort of scientists. A prototype application leverages data available via the Allen Brain Atlas API to integrate, browse and analyze data in an immersive virtual display environment. Key features of the application include presentation of anatomically accurate 3D brain mesh renderings paired with cell representations that can be selected and plotted in a t-SNE graph space. Implementation was done in Unity 5.x with C# and designed for the HTC:VIVE VR headset. The anatomical reference framework is the annotated adult mouse brain (Allen Mouse Common Coordinate Framework; CCF), coupled with spatially precise mappings of single neurons from visual cortex. These representations are paired with in vitro biophysical data from slice recordings and morphological neuron reconstructions, which can also be accessed in the public database online at celltypes.brain-map.org. The mouse brain volume (CCF) is the anchor of the interactive space, from which selected neurons within the brain can be explored, and the ontologically-labeled anatomy of the brain can be manipulated using natural gestures. Preliminary feedback suggests that naive users comprehend spatial and quantitative data relationships quickly and intuitively with immersive data visualization. We continue to investigate how this type of browsing experience, combined with primary data access, facilitates insight into brain function and expands knowledge by innovative experiential media.

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Poster

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Support: NSF EPSCoR Grant 1632738

Title: HyperTools: A python toolbox for visualizing and manipulating high-dimensional neural time-series data

Authors: *A. C. HEUSSER[1], K. ZIMAN[2], L. L. W. OWEN[2], J. R. MANNING[2]
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Abstract: Data visualizations can reveal trends and patterns that are not otherwise obvious from the raw data or summary statistics. While visualizing low-dimensional data is relatively straightforward (for example, plotting the change in a variable over time as (x,y) coordinates on

a graph), it is not always obvious how to visualize high-dimensional datasets in a similarly intuitive way. Here we present HyperTools, a Python toolbox for visualizing and manipulating large, high-dimensional datasets. Our primary approach is to use dimensionality reduction techniques to embed high-dimensional datasets in a lower-dimensional space, and plot the data using a simple (yet powerful) API with many options for data manipulation (e.g. hyperalignment, clustering, normalizing, etc.) and plot styling. The toolbox is designed around the notion of data trajectories and point clouds. Just as the position of an object moving through space can be visualized as a 3D trajectory, HyperTools uses dimensionality reduction algorithms to create similar 2D and 3D trajectories for time series of high-dimensional observations. The trajectories may be plotted as interactive static plots or visualized as animations. These same dimensionality reduction and alignment algorithms can also reveal structure in static datasets (e.g. collections of observations or attributes). We present several examples using various brain imaging modalities (MEG, EEG, ECoG, fMRI) to showcase how using our toolbox to explore the brain through trajectories and low-dimensional embeddings can reveal deep insights into the structure of dynamic neural patterns.

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